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REVIEW

Atrial fibrillation and gastroesophageal reflux disease: the cardiogastric interaction

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Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity and mortality. Multiple conditions like hypertension, heart failure, diabetes, sleep apnoea, and obesity play a role for the initiation and perpetuation of AF. Recently, a potential association between gastroesophageal reflux disease (GERD) and AF development has been proposed due to the close anatomic vicinity of the oesophagus and the left atrium. As an understanding of the association between acid reflux disease and AF may be important in the global multimodal treatment strategy to further improve outcomes in a subset of patients with AF, we discuss potential atrial arrhythmogenic mechanisms in patients with GERD, such as gastric and subsequent systemic inflammation, impaired autonomic stimulation, mechanical irritation due to anatomical proximity of the left atrium and the oesophagus, as well as common comorbidities like obesity and sleep-disordered breathing. Data on GERD and oesophageal lesions after AF-ablation procedures will be reviewed. Treatment of GERD to avoid AF or to reduce AF burden might represent a future treatment perspective but needs to be scrutinized in prospective trials.

Keywords Atrial fibrillation • Gastroesophageal reflux • Autonomic nervous system • Pulmonary vein isolation

Introduction

Atrial fibrillation (AF) is prevalent in 1–2% of the general population, and the number of affected individuals is expected to double or triple within the next two to three decades[1–3] related to the ageing of the population, an inappropriate control of cardiovascular risk factors like hypertension and potentially better treatment options of other conditions like coronary heart disease or heart failure.[4] AF doubles mortality[4–6] and causes marked morbidity[7–9] and reduces quality of life.[10–13] Multiple conditions like hypertension, heart failure, diabetes, sleep apnoea, and obesity play a role for the initiation and perpetuation of AF. Importantly, treatment of these conditions has been shown to prevent recurrence and progression of AF and improve outcome of AF-ablation.[14]

An association between AF and disorders of the gastrointestinal tract has been suggested.[15–18] Particularly due to the close vicinity of the oesophagus and the left atrium, an interaction between oesophageal diseases, e.g. gastroesophageal reflux disease (GERD) and oesophagitis and AF has been proposed. Interestingly, in patients with GERD, episodes of AF triggered by defaecation, abdominal bloating, alcohol, cold water, and fatty food consumption (so called prandial or triggered AF) were reported.[15,16] This temporal relationship further suggests a causal relationship in some of these patients. As understanding of the association between acid reflux disease and AF may be important in the global multimodal treatment strategy to improve outcomes in a subset of patients with AF, we discuss potential GERD-associated arrhythmogenic mechanisms like impaired autonomic stimulation, mechanical irritation due to anatomical proximity of the left atrium, and the oesophagus and local inflammation. Additionally, oesophageal lesions after AF-ablation procedures and the role of proton pump inhibitors (PPIs) will be highlighted.

Anatomic atrial–oesophageal relationship

The posterior wall of the left atrium and the oesophagus are separated by a tissue layer of only ~5 mm. The exact anatomical relationship between oesophagus and atrium is not fixed.[19] It has been reported that oesophagus location is different in computer tomography scans before procedure and during contrast oesophagogram

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during procedures. In some patients, oesophagus is close to left pulmonary vein, while others are close to right pulmonary vein.[20] Oesophageal vessels and lymph nodes as well as the paraoesophageal nerve plexus are located within this tissue layer. The paraoesophageal nerve plexus regulates the motility of the stomach and can branch above or below the level of the left atrium. A representative magnetic resonance image is shown in *Figure 1*.

GERD and AF

The relationship between gastrointestinal symptoms and arrhythmias was first described by Ludwig Roemheld, under the name of 'Roemheld gastrocardiac syndrome', in which an oesophago-gastric stimulus was able to induce arrhythmia-related symptoms.[18] The presence of GERD might increase the risk of AF by 39% in a small-scale population[21] and impact of GERD on incident AF in about 30 000 people from the 1 000 000-person cohort data set sampled from the Taiwan National Health Insurance database has been demonstrated.[22] GERD was independently associated with an increased risk of future AF within 3 years in this nationwide population-based cohort (HR 1.31; 95%, CI 1.06–16.1).[22] On the contrary, conflicting results were reported by using a self-report questionnaire to assess the frequency of GERD in 5288 residents of Olmsted County.[23] Herein, GERD was not associated with risk of AF after adjustment for other risk factors. However, acid reflux disease significantly increased the risk of AF only in the presence of oesophagitis (HR 1.94, 95% CI 1.35–2.78).[23]

Additionally, some studies have demonstrated that gastric acid suppressive therapy by PPIs may help to ameliorate symptoms associated with AF and also facilitate conversion from AF to sinus rhythm in a subset of patients indirectly suggesting a causal relationship. In 18 patients with GERD and paroxysmal AF who complained of retrosternal and epigastric pain, treatment with PPIs either completely stopped or decreased the frequency of AF episodes.[17] In a pilot study, PPI therapy led to a decrease in AF symptoms in 78% of cases with AF and reflux oesophagitis and the antiarrhythmic drug treatment could be discontinued in 28% of the patients.[24] In patients with GERD undergoing simultaneous Holter ECG and 24 h pH monitoring, all patients on PPI treatment showed a reduction in arrhythmia burden.[25] The relationship between GERD and the arrhythmia and the efficacy of PPIs on symptoms of GERD and arrhythmias was validated with questionnaires and endoscopy to scrutinize the diagnosis of GERD.[26] In this case–control study, 32 patients with GERD and arrhythmias were included. Holter ECG was performed for each patient during oesophageal manometry, acid perfusion, and 24 h pH monitoring. In 56% of all patients with GERD and AF, a correlation between oesophageal pH and heart rate variability was achieved and PPI treatment reduced cardiac-specific symptoms in these patients.[27]

In a prospective case–control study of patients undergoing AF catheter ablation, patients with GERD and/or irritable bowel syndrome were more likely to have self-reported triggered AF (defaecation, abdominal bloating, alcohol, cold water, and fatty food consumption), a positive vagal response during radio frequency catheter ablation and independent firing from pulmonary veins. Electroanatomical mapping, quantifying structural changes in the atrium, revealed no increase in left-atrial scar when compared with age-matched controls.[27] These data suggest that not structural changes in the atrium but autonomic changes associated with the activation of the ganglionated plexi and an increase in focal discharges in the pulmonary veins play the causative role for the initiation and perpetuation of AF in GERD. These data are based on a small sample size. However, the evidence for beneficial antiarrhythmic effects of PPI-treatment comes from small

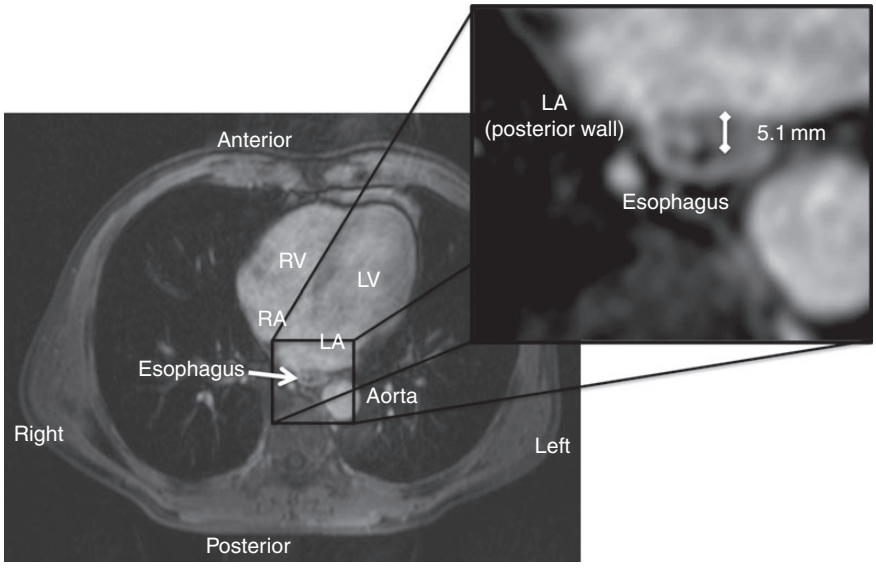

Figure 1 Transverse cross-sectional overview (left) of the thorax at the level of the heart (magnetic resonance imaging). In the right upper figure, the regional relationship between the oesophagus and the posterior wall of the left atrium is depicted. (LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle).

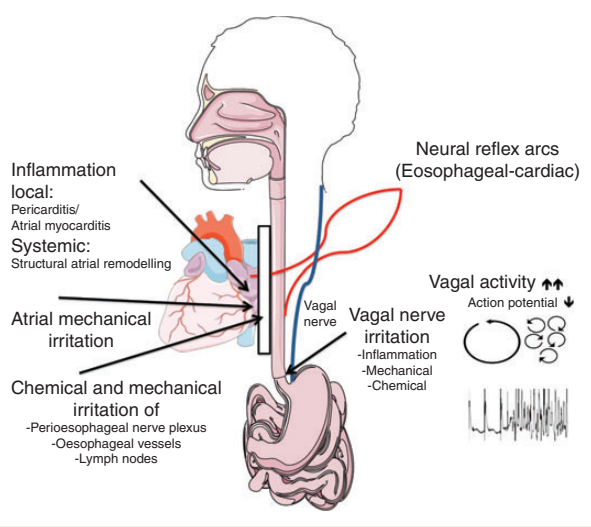

Figure 2 Potentially involved mechanisms for the relationship between GERD and AF. For more details see section on 'Potentially involved mechanisms'.

retrospective and observational studies and requires further validation by large prospective trials.

Potentially involved mechanisms

Figure 2 summarizes the potentially involved mechanisms for the relationship between GERD and AF.

Autonomic activation

Neural reflex arcs from the oesophagus and the heart have been shown in both animals and humans. In humans, chemical, electrical, and mechanical stimulation of the oesophagus modifies the sympathovagal balance.[28] Oesophageal stimulation amplifies respiratory-driven cardiac vagoafferent modulation, while decreasing sympathetic modulation.[28] Oesophageal acid stimulation is further associated with an increase in vagal activity.[29] Acid refluxes cause a local inflammatory process that may directly alter the autonomic innervations of the oesophageal mucosa and may also penetrate the oesophageal wall and stimulate the adjacent vagal nerves. Injury of the distal oesophagus can further impair vagal nerve responses, particularly nerve sensitization of the afferent pathways.[30] These and other considerations suggest the involvement of the cardio-oesophageal reflex in case of GERD associated AF.

Several observations support the relevant role of the autonomic nervous system for the initiation and the maintenance of AF.[31] Studies in lone AF patients and in animal models of intermittent rapid atrial pacing and congestive heart failure have indicated that AF onset is associated with simultaneous sympathovagal activation rather than with an increase in vagal or sympathetic drive alone.[32,33] On the cellular level, cholinergic muscarinergic receptors are the primary mediators of parasympathetic control of heart function. Muscarin-2 receptor (M2R) stimulation with acetylcholine directly activates G-protein-dependent potassium currents leading to a shortening of the atrial action potential duration and atrial effective refractory period.[34] Additionally, the effect of vagal stimulation on atrial refractoriness is heterogeneous because of heterogeneity in the distribution of parasympathetic nerve endings and/or M2Rs. Increased vagal activation, as present in GERD-patients, creates an arrhythmogenic substrate for re-entry and, thereby, increases AF-susceptibility.[31,34]

Inflammation

Observational studies also suggest that not symptoms of GERD in general but more specifically endoscopic evidence of oesophagitis is associated with increased risk for AF and may cause and maintain arrhythmias.[24,25] Propagation of the local inflammatory process through the oesophageal wall may also cause local pericarditis or atrial myocarditis due to the proximity of the oesophagus to the left atrium. In patients with so-called lone AF (AF without structural heart disease), myocarditis can be identified in up to 66%.[35] Circulating inflammatory cytokines have been shown to play a role in the pathophysiology of AF.[34] Inflammation of the oesophageal mucosa affects local receptors that may induce afferent–efferent reflex mechanisms.[36]

Cardiac perfusion

The effect of oesophageal acid stimulation on coronary blood flow was investigated in 14 patients with angiographically documented significant coronary artery disease and in 18 heart transplant recipients. Oesophageal acid stimulation can cause anginal attacks and significantly reduce coronary blood flow in patients with coronary artery disease. The lack of such an effect in heart transplant recipients with complete heart denervation suggests the involvement of a neural reflex.[37] While ventricular ischaemia impacts left-ventricular contractility and relaxation, reduced cardiac perfusion may also affect atria predisposing to structural alterations including myocyte loss and scaring leading to substrates for atrial arrhythmias.[38]

Hiatus hernia

Hiatus hernia is associated with increased occurrence of GERD symptoms.[39] Whether the presence of hiatus hernia further increase the risk of AF is unknown. A hiatus hernia as well as an intrathoracic stomach, representing the end stage of a hiatal hernial diaphragm, has the potential to mechanically irritate the left atrium. Additionally, the hernia may increase reflux and, thereby, result in oesophagitis accompanied by AF. The association between hiatus hernia and atrial tachyarrhythmias has been described as increases in atrial ectopic beats upon swallowing in a patient with a big hiatus hernia.[40] Interestingly, there are case reports that repair of a large paraoesophageal hernia[41] or an intrathoracic stomach[42] can suppress paroxysmal atrial arrhythmias.

Comorbidities: obesity and sleep-disordered breathing

Comorbidities like obesity and sleep-disordered breathing[43] are highly prevalent in GERD-patients and may be associated with the development of AF by systemic changes related to these conditions.

There is a 3–8% higher risk of new AF-onset with each unit increase in body mass index, and this association is independent of other cardiovascular risk factors.[5] Pericardial fat is associated with the occurrence of AF, persistence of AF, left-atrial enlargement, and worse outcomes of AF ablation.[44] Additionally, obesity results in progressive atrial structural and electrical remodelling. In sheep, following a high-calorie diet, obesity was associated with atrial

electro-structural remodelling, increased atrial size, changes in conduction, and more persistent AF episodes. Obesity was associated with reduced posterior left-atrial endocardial voltage and infiltration of contiguous posterior left-atrial muscle by epicardial fat.[45] Whether the anatomical proximity of the posterior wall of the left atrium and the oesophagus play a role for the development of this potential substrate for AF is unknown. In obese patients, risk factor management according to American Heart Association/American College of Cardiology guidelines improved the long-term success of AF ablation.[46,47]

Besides obesity, sleep-disordered breathing is frequently diagnosed in patients with GERD symptoms. The prevalence of GERD in obstructive sleep apnoea (OSA) patients is significantly higher than the general population[48,49] and treatment of OSA has been shown to improve symptoms of GERD.[50] In patients with OSA, ineffective inspiration against the occluded upper airways during obstructive respiratory events cause intrathoracic pressure swings.[51] This may impact the sphincter function of the oesophagus, increasing the occurrence of GERD. OSA can also result in myocardial stretch of the heart chambers and changes in transmural pressure gradients.[51] Obstructive respiratory events are associated with intermittent apnoea-associated hypoxaemia and hypercapnia as well as sympathetic activation and subsequent haemodynamic fluctuations.[52] Long-term OSA has been shown to be associated with atrial remodelling characterized by atrial enlargement and local conduction disturbances in patients with AF.[53] Additionally, acute obstructive respiratory events cause pronounced shortening in atrial refractoriness and result in increased occurrence of spontaneous premature atrial contractions, representing potent triggers for spontaneous AF-episodes in a pig model for OSA and humans.[54] Treatment of sleep-disordered breathing in AF-patients reduces recurrence of AF after electrical cardioversion[55] and improves outcome after pulmonary vein isolation.[56,57,58] Although nocturnal gastroesophageal reflux has been observed in patients with OSA, no coincidence and sequence in time of arousal, apnoea, and reflux events could be identified in a previous mechanistic clinical study.[59]

The true role of comorbidities like obesity and sleep-disordered breathing, and whether interventions like weight loss or sleep apnoea-treatment, experience antiarrhythmic effects by affecting GERD in AF-patients is speculative and need to be investigated in future studies.

Inflammatory bowel disease and coeliac disease

Besides GERD, also other conditions of chronic inflammation like inflammatory bowel disease may be associated with increased AF-occurrence.[60] Inflammation activity, which is enhanced in chronic inflammatory bowel disease, may play a role in the development of AF. Active inflammatory bowel disease is associated with increased risk of AF and stroke.[60,61] One study showed an increase in electrocardiographic P-wave dispersion in patients with inflammatory bowel disease, which is considered an AF risk factor.[62]

AF is more common both before and after coeliac disease diagnosis in patients with coeliac disease though the excess risk is small.[63] However, in a population-based study of patients with coeliac disease, failed mucosa healing was not associated with an increased risk of AF.[64] Echocardiographic studies revealed a more pronounced atrial remodelling in patients with coeliac disease, characterized by slower atrial electrical conduction and higher atrial electromechanical delays,[65] while atrial mechanical function was preserved.[66] Potential explanations for the increased risk of AF in coeliac disease include chronic inflammation and shared risk factors.

Additional studies are needed to clarify the link between AF and conditions of chronically increased inflammation like inflammatory bowel disease and autoimmune diseases such as coeliac disease.

Conclusions

Clinicians should be aware of the possible cardiogastric interaction with GERD being associated with AF. Identification and appropriate treatment of GERD, especially oesophagitis, may help to reduce AF-onset and -symptoms and can facilitate conversion from AF to sinus rhythm in a subset of patients. Further prospective and well-designed studies are needed to determine whether (i) there is a true causal relationship, independent of comorbidities like obesity and sleep-disordered breathing, (ii) the PPI treatment can reduce AF-related symptoms and progression of AF, and (iii) other chronic gastrointestinal diseases like inflammatory bowel disease and coeliac disease play a role for the development of an arrhythmogenic substrate in the atrium.

Conflict of interest: none declared.

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