Prophylactic Proton Pump Inhibition After Atrial Fibrillation Ablation

Is There any Evidence?

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Authors and Disclosures

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Abstract and Introduction

Abstract

The development of an atrio-oesophageal fistula following catheter ablation for atrial fibrillation is a well known, but rare complication with a high mortality, partially due to the late fistula formation weeks after the initial procedure. Technical measurements are undertaken to avoid oesophageal damage during catheter ablation of atrial fibrillation, yet, oesophageal and mediastinal lesions occur in a substantial number of patients following pulmonary vein isolation. This has led to prophylactic use of proton pump inhibitors in many centres. Current guidelines and consensus reports list no objectives on this issue. The aim of the paper is therefore to review current clinical and experimental evidence for this treatment.

Introduction

Catheter ablation is an accepted treatment option in patients suffering from symptomatic atrial fibrillation (AF). A rare, but dreaded complication of this intervention is the development of an atrio-oesophageal fistula. Surveys on catheter ablation of AF report a rate of 0.04% of fistula formation with a mortality of ~75%. Symptoms often include fever, dysphagia, and fluctuating neurological deficits. Surgical treatment is the first-line therapy in spite of single case reports of interventional oesophageal stenting. Nevertheless, mortality remains high, partially due to the late fistula formation, weeks after the initial procedure and the often delayed diagnosis. Various measurements like oesophageal temperature monitoring are undertaken to avoid oesophageal damage during catheter ablation of AF. However, oesophageal and mediastinal lesions occur in a substantial number of patients following pulmonary vein isolation. This has led to prophylactic use of proton pump...
inhibitors (PPIs) in many centres. Yet, current guidelines and consensus reports list no objectives on this issue. The aim of the paper is therefore to review current clinical and experimental evidence for this treatment.

**Pathophysiology and Experimental Evidence**

A key feature of fistula formation following left atrial ablation is the delayed occurrence. Hence, mechanical injury is unlikely to play a pivotal role in the pathophysiology of this process. Both components – the posterior wall of the left atrium and the anterior oesophagus – may be weakened by the endocardial catheter ablation. Presumably, thermal damage to the anterior oesophageal arteries and consecutive ischaemic lesions especially of the mucosal layers of the oesophagus may explain the deferred fistula development. Compared with the low rate of atrio-oesophageal fistula, the high prevalence of mucosal changes following left atrial ablation is striking. Endoscopic follow-up evaluations showed in these studies resolution of the initial lesions. Nevertheless, there is evidence of a causal relationship of oesophageal ulcerations and later perforation ultimately culminating in a fully formed fistula. Gastrooesophageal reflux aggravating mucosal injury as a kind of two-hit phenomenon may play an additional role. This is supported by a canine study by Yokoyama et al., who observed the development of atrio-oesophageal fistula in two animals following ultrasound ablation after previous severe oesophagitis and ulceration. Impairment of the lower oesophageal sphincter due to damaged vagal fibres and thereby pronounced gastrooesophageal reflux may be the pathophysiological background.

**The Potential Role of Proton Pump Inhibitors in Ablation Induced Oesophageal Fistula Formation**

Proton pump inhibitors are widely prescribed since their advent for acid-peptic disease with sales totaling $13.6 billion worldwide in 2009. In gastrooesophageal reflux disease, PPIs are highly effective due to reducing the acidity of the gastric juice and therefore allowing a healing of oesophagitis. As discussed above, gastrooesophageal reflux seems to play a potential role in formation of ablation-induced oesophageal ulcer and fistula formation. Therefore, it seems in our opinion reasonable to use a prophylactic PPI therapy in all patients who undergo AF ablation to reduce the potential additional risk of fistula formation due to acid gastrooesophageal reflux.

Apart from gastrooesophageal reflux disease, PPIs are also effective in reducing the size of iatrogenic induced ulcers. Thus, PPI therapy maybe also helpful in reducing the size of postablation-induced ulcers.

**Clinical Evidence**

Experimental data are supported by clinical evidence. Several case reports specified the oesophagus as the initial site of perforation. Recently, Grubina et al. observed a pneumopericardium following radiofrequency ablation for AF after perforation of the oesophagus and the oblique pericardial sinus. Of note, the posterior wall of the left atrium was not affected. Similarly, Vijayaraman et al. reported an oesophageal perforation with pericardial and mediastinal drainage despite monitoring the oesophageal location by barium swallow, intracardiac echocardiography, luminal oesophageal temperature.
monitoring and, noteworthy, despite prophylactic PPI therapy. Gilcrease et al. showed by serial computed tomography chest scans progressive ulceration of the oesophagus, connection to the mediastinum and the pericardial space, and ultimately perforation of the left atrium 41 days after the initial ablation procedure. Endoscopic evaluation of the oesophageal ulceration was not performed. Using a robotic navigation system, Tilz et al. also reported a high incidence of thermal oesophageal injury including a perforation. Oesophageal stent implantation using a covered stent was performed successfully and follow-up showed no atrio-oesophageal fistula. Therefore, nearly 3 months after the ablation procedure, the stent could be removed. In this case, this oesophageal (most likely) covered perforation became symptomatic after stopping the routinely prescribed PPI 10 days after ablation.

Data on the development of gastrooesophageal reflux in patients undergoing AF ablation remains controversial. Schmidt et al. observed a positive correlation of reflux-like symptoms and endoscopically diagnosed oesophageal wall changes following radiofrequency ablation for AF. Martinek et al. studied 31 patients undergoing radiofrequency ablation for AF using a leadless pH-metry capsule. A substantial number of patients (5/26, 19.2% respectively) without reflux prior to ablation acutely developed gastrooesophageal reflux diagnosed by a pathologic DeMeester score. On the other hand, Nölker et al. were unable to show an increase of the DeMeester score, but rather noticed a decrease in reflux episodes despite a higher incidence of mucosal oesophageal lesions compared with the study by Martinek et al.

**Mechanism of Proton Pump Inhibitors**

As prodrugs, PPIs require activation to bind irreversibly to the canalicular H\(^+\)/K\(^+\)-ATPase of secreting parietal cells in the stomach. Activation is only possible in the presence of gastric acid. By blocking the ATPase, the exchange of hydrogen for potassium is prevented and acid production is prohibited. Apart from the stomach, other parts of the body do not supply low enough pH levels for the activation of PPIs. Metabolism takes place in the liver—primarily by cytochrome P450 (CYP2C19) enzymes—and metabolites are excreted by urine and stool. Effective acid inhibition lasts for about 10–14 h after administration of an appropriate dosage of a PPI.

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**Risk–Benefit Consideration: Drug Safety**

When considering a prophylactic therapy with PPIs, the safety profile of these drugs needs to be taken into account. Some observational studies raised concern of a reduced effectiveness of clopidogrel when coadministered with PPIs, since these substances competitively inhibit cytochrome P450 (CYP2C19), which activates the prodrug clopidogrel.\(^2\) However, more recent data from a large registry could not confirm this negative interaction. Proton pump inhibitor use was not associated with an increased risk of cardiovascular events or mortality, whatever genotype of CYP2C19 was present.\(^3\) Therefore, clopidogrel therapy and concomitant PPI use seem to be safe in clinical practice. Besides, catheter ablation for AF should be postponed until antiplatelet therapy with clopidogrel, e.g. after stent implantation, is no longer necessary to avoid bleeding complications.\(^4\) Other potential side effects of PPIs may include imbalances in levels of vitamins and minerals and increased risk for infections due to a reduced acid-mediated barrier, although data concerning these concerns are controversial.\(^5-8\) Apart from that, the other side effects reported occur during long-term PPI therapy and are therefore negligible during short-term therapy after catheter ablation for AF.

**Clinical and Future Perspective**

In summary, there is some experimental and clearly limited clinical evidence of progressive oesophageal injury rather than atrial lesions as the site of ‘break-through’ in the process of atrio-oesophageal fistula formation. Gastroesophageal reflux might serve as an additional factor not only by preventing healing of ulcerations but even promoting this phenomenon. Yet, other mechanisms such as traumatic perforation of the weakened oesophageal wall, which are not influenced by PPI therapy, may also play a potential role in fistula formation. Thus, avoidance of unnecessary ablation with too much power and pressure at the posterior wall of the left atrium as the trigger for the whole process remains of paramount importance. Besides, patients and their treating general practitioners need to be informed about early signs of atrio-oesophageal fistula formation, with special regard on the potentially delayed onset of symptoms. Transoesophageal echocardiography and endoscopy should be avoided, because oesophageal perforation might be aggravated and air embolism promoted. In addition, each patient with suspected atrio-oesophageal fistula should be referred to a centre with appropriate surgical facilities.

Nevertheless, given the excellent safety profile and good tolerance of PPIs, prophylactic short-term use after catheter ablation for AF is in our opinion justified. Assessment of the effect of PPIs on mucosal lesions needs to be investigated in large randomized trials. However, due to the low rate of atrio-oesophageal fistula, a protective role on fistula formation is unlikely to be detected in randomized studies. Until then, PPI therapy remains at the treating physicians decision.

**References**

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