Complications of Atrial Fibrillation Ablation When Prevention Is Better Than Cure

Authors and Disclosures

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Abstract

As atrial fibrillation ablation is becoming increasingly popular in many cardiac electrophysiological laboratories around the world, preventing, avoiding, or treating procedure-related complications is of utmost importance. In our review of the literature regarding this issue, we addressed in detail all the potential collateral and undesired effects associated to this intervention.

Introduction

Pulmonary vein isolation (PVI) is a well-known option for the treatment of both paroxysmal and persistent atrial fibrillation (AF).[1] The lack of new effective antiarrhythmic drugs and the side effects linked to the acute and chronic use of the old ones have favoured the development and the implementation of AF catheter ablation, which, nowadays, can be obtained with different strategies and/or technologies.[1]

Since its first introduction in the cardiological context in the late nineties,[2] the technique, which allows electrical isolation of pulmonary vein muscle sleeves from the left atrium, has improved by leaps and bounds. Although this good news, complications are still present and cannot be ignored. Plenty of literature has already been produced on the description and the characterization of the complications of AF ablation, as well as on their management.[1] Taking this in mind, the aim of this review is to list them briefly but, above all, to describe possible strategies to reduce their incidence. The present manuscript does not want to substitute the more authoritative and reliable publications on the topic,[1,3] but, more simply, to increase the awareness on a topic that could be easily underestimated or ignored by the younger and less-experienced cardiac electrophysiologists.

A worldwide survey on the methods, efficacy, and safety of AF catheter ablation recently published by Cappato et al.[4] revealed that the indications for AF catheter ablation have been progressively widened. Today, AF catheter ablation is offered to a wider number of patients compared with the first years of its clinical application. This could explain why the overall success of the procedure has not increased significantly and why complication rates including the incidence of iatrogenic flutter has not decreased

despite the great improvement in both the experience of the operators and the accuracy of the principal mapping systems used during AF catheter ablation.

Complications of AF ablation express themselves through very different clinical scenarios which vary from local issues (related to the percutaneous access which precedes catheter ablation) to life-threatening conditions. According to the most recent international guidelines on AF ablation,[1] 'a major complication is defined as a complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization'.

An outstanding contribution to the description and quantification of complications of AF ablation has been given by three different groups of authors.[5–7] Complication rates varied from a minimum of 0.8% to a maximum of 5%. No periprocedural deaths were reported in any of these studies. Interestingly, treatment with clopidogrel, female gender and AF ablations performed in July or August were independent predictors of vascular complications, whereas advanced age and female gender predicted the occurrence of major adverse events. The only predictor of cardiac tamponade was prior radiofrequency AF catheter ablation.

In the most recent worldwide survey by Cappato *et al.*, complications have been observed in 4.5% of patients undergone AF ablation. Death accounted for 0.15% of total complications, whereas atrio-oesophageal fistula happened in 0.04% of procedures. Cardiac tamponade complicated 1.31 % of total procedures. Stroke occurred in 0.23 %, transient ischaemic attack in 0.71% and PV stenosis requiring surgical or percutaneous dilation in 0.29%. Among minor complications, total femoral pseudoaneurysms accounted for 0.93% whereas total artero-venous fistulae have been observed in 0.54% of the total procedures. Iatrogenic atrial flutters were almost doubled compared with the first survey performed by the same group of investigators between 1995 and 2002.

Each complication will be treated in turn.

Death

Death is an infrequent complication of AF catheter ablation. As showed by Cappato *et al.*,[8] peri-procedural death incidence observed in catheter ablation of AF does not differ from the incidence of peri-procedural death in catheter ablation of supraventricular tachycardias.[9,10] Nevertheless, it is also true that a scientific estimation of the causes leading to death during or after an AF catheter ablation is often prejudiced by the very small number of events and/or by the reticence of the operators to go into details when such an event occurs.

Many are the factors which can turn complications occurring during or after AF catheter ablation into death: the need of a transseptal puncture to reach the left atrium and the PV ostia, the handling and manipulation of catheters in the left atrium and the association of radiofrequency-dependent lesions in the left atrium with very high levels of anticoagulation. On this subject, very recently, two independent groups of investigators have demonstrated in a swine cardiac model that the probability of cardiac perforation is directly proportional to the contact force exerted by ablation catheters on cardiac walls and that radiofrequency energy reduces by some extent the minimal contact force needed to perforate the heart.[11,12] New ablation catheters able to detect beat by beat contact force will be very soon available and will help electrophysiologists both in understanding the real impact of the handling of catheters on cardiac tissues and hopefully in avoiding any type of cardiac rupture.

Cardiac tamponade (both acute and/or late) has demonstrated to be the most common fatal complication leading to cardiac arrest during or after AF catheter ablation, followed by development of atrio-oesophageal fistulas. Ischaemic brain or cardiac insults are the third most frequent causes of death followed by extrapericardial bleedings related to subclavian or PV perforation and by post-operative massive pneumonia refractory to antibiotics. Less represented and also less specific are deaths related to conditions such as torsade de pointes, sudden respiratory failure, or acute respiratory distress syndromes in the post-operative context. The strategy adopted to perform PVI (CARTO-guided vs. Lasso-guided or irrigated tip ablation vs. 4 mm tip ablation) seems not to affect the incidence of death during or after AF catheter ablation.[13] Even if it seems that also centre experience does not influence the rate of death related to AF catheter ablation, in our opinion it is far safer to have an AF ablation procedure performed at a referral centre than in a community hospital with little experience.

Esophageal Injury/Atrio-oesophageal Fistula

Atrio-oesophageal fistula is a very rare complication of AF catheter ablation. Described for the first time in two very experienced centres in 2004,[14,15] this complication is the most dreadful and lethal among all the others related to AF catheter ablation. Its clinical presentation is extremely variable: patients with an atrio-oesophageal fistula could present with a variety of signs and symptoms such as chest pain, heartburn, dysphagia, anorexia, and haematemesis immediately after or also late after the index procedure. Usually death occurs because of cerebral or myocardial air embolism, endocarditis, massive gastrointestinal bleeding and septic shock.[16] Surgical cardiac and oesophageal repair are mandatory to increase the survival in these patients; therefore, a rapid diagnosis is highly desiderable. To this aim, cardiac computed tomography is the most indicated while endoscopy has to be avoid for the high risk of worsening the damage on the oesophageal walls. Interestingly, Bunch *et al.*[17] have proposed a temporary oesophageal stenting as a possible non-surgical treatment of this complication, able to warrant the complete healing of the damaged oesophageal wall.

Even more desiderable is avoiding the occurrence of an atrio-oesophageal fistula. To this aim, a lot of studies sought to investigate the physiopathologic mechanism underlying this complication. As demonstrated by computed tomography,[18] cardiac magnetic resonance,[19] intracardiac echocardiography,[20] the strict anatomic relationship between the left atrium and the oesophagus together with the delivery of radiofrequency energy on the posterior wall of the left atrium are the principal causes leading to the occurrence of atrio-oesophageal fistula or, more generally, of oesophageal injury. Interestingly, Meng *et al.*[21] have demonstrated that new oesophageal late gadolinium enhancement is present in almost one-third of patients after PVI and this finding is irrespective of the type of catheter ablation (irrigated vs. not-irrigated tip) used during the procedure, of ablation time, of anatomical location of the oesophagus compared with the left atrium, of the size of left atrium cavity or of the timing of cardiac magnetic resonance study after PVI.

Different strategies can be adopted to avoid or reduce the incidence of this dreadful complication. First of all, localization of the region of contact between left atrium and oesophagus can be obtained before the procedure itself by means of computed tomography after a barium swallow or magnetic resonance after a barium plus gadolinium diglutamate swallow[22] or during the ablation procedure with intracardiac echocardiography.[23] Moreover, electroanatomical mapping systems such as CARTO™ (Biosense Webster, Diamond Bar, CA, USA) and NavX™ (St Jude Medical, Sylmar, CA, USA) allow the superimposition of the oesophageal imaging obtained with the Carto SoundStar™ probe or with the NavX™ itself with the real-time electroanatomical map of the left atrium.[24,25] Secondly, it is strongly advisable to avoid delivery of high levels of radiofrequency energy on the posterior wall of the left

atrium or on the posterior aspect of the PV antra, usually areas of presumable contact with the oesophagus. To this aim, since theoretically radiofrequency energy exerts a rise in local temperatures, it's common practice in many centres to monitor the oesophageal temperature with an oesophageal probe[26,27] to titrate the radiofrequency energy application on the areas at potential risk of oesophageal injury and to stop radiofrequency energy delivery when a rapid elevation of the oesophageal internal temperature is recorded. In centres which do not perform cardiac computed tomography or cardiac magnetic resonance before the procedure, the use of oesophagram with water soluble contrast may represent a valid trick to avoid ablation on portions of the left atrium in close vicinity of the oesophagus.

However, the main issue related to this practice is the lack of knowledge of what has to be considered the 'safest' amount of radiofrequency energy. Indeed, the accuracy of luminal temperature monitoring to estimate the oesophageal heating and then in anticipating the formation of the oesophageal injury is uncertain.[28] Poor correlation between oesophageal internal temperature and total radiofrequency energy delivery has been demonstrated in initial clinical studies.[20,29] Interindividual variability in oesophageal and posterior left atrial wall thickness may explain this finding along with a presumable lack of fidelity of the luminal probe in measuring the heating of the oesophageal wall. Furthermore, as brilliantly evidenced by Nakagawa,[30] oesophageal tissue heating and consequent injury seem to be related more to the catheter tip-tissue contact force rather than to the total amount of radiofrequency energy delivered for PVI.

There's no compelling evidence that any strategy employed can reduce or even avoid this complication although many are used. The most common measures adopted in this context are reducing the power and the duration of radiofrequency energy delivery near or over the oesophagus (25 W is usually considered safe) as well as monitoring the oesophageal temperature by means of an endoscopic probe. Another very simple and intuitive option is to avoid any radiofrequency delivery at the posterior left atrial wall, as to the best of our knowledge, there is no conclusive evidence that linear lesions in this region would improve late outcome as compared with accurate, stable (i.e. long-lasting) PV isolation in whatever AF form (i.e. paroxysmal, persistent, and permanent). The empiric use of proton-pump inhibitors after ablation to mitigate reflux that has been observed in many cases and correlated with pH studies after ablation.[31] Questionable is also the clinical utility of a cooled saline-irrigated balloon inside the oesophageal lumen during AF catheter ablation.[32] Indeed, if on the one hand cooling of the internal lumen of the oesophagus should limit the transmural rise of the temperature, on the other hand inflation of a balloon device inside the oesophagus could increase the area of contact with the left atrium, enhancing paradoxically the heat transfer and the chances of thermal injury.

The majority of atrio-oesophageal fistulas described in the literature has been related to radiofrequency energy delivery. A possible and well-known alternative to radiofrequency is cryothermal energy. Used first for surgical treatment of ventricular arrhythmias and then for endocardial treatment of specific supraventricular arrhythmias, very recently cryothermal energy indication has been enlarged to include also AF or left atrial tachycardias.[23] Cryothermal energy can be delivered focally through traditional deflectable ablation catheters or circumferentially through innovative inflatable balloons with proven efficacy.[1] Unfortunately, as radiofrequency energy, cryothermal energy induces a conductive heat transfer on the oesophagus, resulting in an equivalent amount of oesophageal injury compared with radiofrequency.[33] There's evidence in animal models that cryothermal ablation could determine a transmural injury of the oesophagus but, unlike radiofrequency energy which produces necrosis and ulcers, it preserves the architecture of the cells reducing at great extent the probability of a fistula or of ulceration.[28] Even though contrasting data have been produced on the risk of oesophageal ulcerations after cryoballoon ablation,[34,35] cryothermal energy could represent at the moment a valid alternative to

radiofrequency energy when ablation of the posterior wall is needed and hybrid approaches to AF catheter ablation has already been proposed.[36]

Haemorrhagic Complications

Haemorrhagic complications include major and minor bleedings. Cardiac tamponade has to be considered a major bleeding and is by far the most common major complication of AF catheter ablation. Other major bleedings should be considered any haematoma which requires intervention, the need of transfusion, massive haemoptysis, haemothorax, and retroperitoneal bleeding. Minor bleedings has to be considered any kind of haematoma or bleeding which does not require intervention or which remains asymptomatic. Femoral pseudoaneurysms and femoral arterovenous fistula are included in haemorrhagic complications and could cause, accordingly to their extent, major or minor bleedings.

Cardiac Tamponade

Different physiopathologic mechanisms lead to cardiac tamponade during and after PVI. Among the others, main cofactors in this clinical context must be considered the transseptal puncture[37] and ablation-related damage to the left atrium.[1]

Transseptal puncture represents an inevitable vulnerability to the heart during AF ablation procedures. Current transseptal puncture technique is very similar to the first initial reports in late 50s.[38] Briefly, after being inserted into a long sheath and set against the fossa ovalis, a needle is used to puncture the septum to enter the left atrium. Safety of transseptal puncture lies in the recognition of the right atrial anatomy and in particular of the fossa ovalis. Very recently, Sy *et al.*[39] provided a very interesting overview on the technique of the transseptal puncture and at the same time proposed a very promising 'problem-based stepwise approach', helpful in troubleshooting difficult left atrial transseptalizations and hopefully also in reducing the incidence of cardiac perforation. The authors reinforced the utility of intracardiac echocardiography or transoesophageal echocardiography in those procedures in which right atrial anatomy is unusual or in which fossa ovalis is difficult to engage. Transoesophageal echocardiography is often poorly tolerated and requires deep sedation or general anaesthesia; intracardiac echocardiography is associated with increased costs and needs a precise expertise. A third possibility has been recently proposed by Mitchell-Heggs *et al.*[40] and consists in guiding transseptal puncture in patients not under general anaesthesia using an intracardiac echocardiography probe positioned intranasally into the oesophagus.

Left atrial linear ablations are also associated with a higher incidence of cardiac tamponade.[41] Hsu *et al.*[42] not only confirmed this finding but found also a significant correlation of cardiac tamponade with 'popping', a well-known physical phenomenon related to the sudden boiling and consequent rupture of the endocardial tissue exposed to high levels of radiofrequency energy. However, radiofrequency energy is not the only cause of cardiac rupture: contact force is another relevant cofactor and many studies conducted in preclinical field corroborated this finding.[7,8,43] Indeed, Yokoyama *et al.*[43] developed an open-irrigated ablation catheter able to measure contact force: interestingly, they found that not only radiofrequency energy lesion size but also steam pop and thrombus incidence are strictly depending on contact force exerted by the ablation catheter on the interface with cardiac tissue. Hopefully, the introduction on the market of these new catheters will allow a safer ablation of cardiac tissues and a reduction in the incidence of cardiac tamponade or rupture.

Some warning should be raised for late cardiac tamponade. Even if there's no clear-cut definition for it, delayed cardiac tamponade has been described.[3] Taking this into account, extreme attention should be given to signs and symptoms such as agitation, tachycardia, oligouria in patients undergone a recent AF ablation.

Speaking more generally about AF-ablation-related bleeding, an increasing amount of data has been produced in the last few years to clarify which should be adopted as optimal anticoagulation management before and after PVI. Most significant contributions in this field belong to the same group of investigators, who demonstrated that periprocedural administration of warfarin is safe and efficacious[44] and may reduce thromboembolic events without increasing the risk of haemorrhagic complications (including major and minor bleedings).[45] Future randomized international multicentre trials should confirm if the standard protocol of anticoagulation (which usually includes discontinuation of warfarin 3–5 days before the procedure and bridging with low-molecular weight heparins before and after the procedure along with restoration of warfarin) should be modified.

Thromboembolic Events

Many studies have investigated the incidence of thromboembolic events (including transient ischaemic attacks and major strokes) during or after AF catheter ablation. The introduction of open-irrigated catheters and the use of early and aggressive heparinization have reduced significantly the risk of cerebrovascular events related to the procedure,[46–48] even though is not clear if the benefit is shifted more towards late cerebrovascular events than the periprocedural ones. Even though Scherr *et al*.[49] evidenced an incidence of 1.4% of periprocedural thromboembolic events using an open-irrigated catheter, more robust data are needed to demonstrate a benefit of these catheters over the non-irrigated 4 mm ones. On the other hand, a multicentre retrospective study examined rates of stroke after catheter ablation of AF and, surprisingly, over a follow-up of about 2 years and a half, no difference in thromboembolic events was noted between patients who withdrew oral anticoagulation and patients who continued to be anticoagulated.[50]

As evidenced in studies using intracardiac echocardiography,[41–43] activated clotting time >300 s and high-flow perfusion of the transseptal sheath are mandatory to reduce thromboembolic complications during AF catheter ablation. Furthermore, as already-stated above,[40] continuous administration of warfarin all along the procedure without bridging with low-molecular weight heparins could help in reducing the incidence of stroke and transient ischaemic attacks without affecting the number of bleeding complications.

To complicate matters further, a recent study by Gaita *et al*.[51] aimed to assess the thromboembolic risk (both silent and clinically evident) associated with AF catheter ablation using pre- and post-procedural cerebral magnetic resonance imaging. The authors reported an incidence of clinically manifest thromboembolic events comparable to what was already demonstrated in the previous studies on the topic (0.4%), but, at the same time, evidenced clinically silent embolic lesions in 14% of patients undergone AF catheter ablation. Anticoagulation degree and electrical or pharmacological cardioversion during the procedure were significantly correlated with silent cerebral embolism.

Open questions remain still on the way. Indeed, further studies are needed to assess any potential increase or decrease of thromboembolic risk associated with 'one-size-fits-all' devices such as a cryoballoon, laser balloon, Mesh™ ablator or Ablation Frontiers™ ablator. To this aim, the MACPAF study will compare the efficacy and the safety of cryoballoon ablation vs. mesh ablation in patients with

drug-refractory paroxysmal AF.[52] Furthermore, it is still unknown if therapeutic international normalized ratios, which demonstrated to reduce the incidence of periprocedural stroke,[40] could also replace completely full intraprocedural heparinization

Pulmonary Vein Stenosis

Occurring in 1–3% of cases, PV stenosis after AF catheter ablation was first described in 2000.[53] As stated in the guidelines,[1] 'according to the percentage reduction of the luminal diameter, the severity of PV stenosis is generally defined as mild (<50%), moderate (50–70%), or severe (>70%)'. The real incidence of PV stenosis has further decreased under 1%, thanks to the progressive shift of the site of ablation from the internal portion of the veins towards the PV antrum and thanks to the great improvement in spatial accuracy of the most used mapping systems.[54] Pulmonary vein stenoses are often clinically silent; symptoms are extremely variegated and may include cough, dyspnea, chest pain, haemoptysis, and recurrent respiratory infections.[49] Severity of the clinical presentation relies on the entity of the stenosis and the number of PVs involved.[55] Since the clinical picture associated with PV stenosis is extremely variable, PV stenosis should be suspected in every patient presenting with one the above clinical symptoms after an AF catheter ablation. Cardiac computed tomography and cardiac magnetic resonance are the diagnostic tools commonly used to make the diagnosis; transthoracic, or transoesophageal echocardiography could help only partially but might be useful to assess pulmonary vein flows.[50] Radionuclide ventilation/perfusion imaging may serve also as a screening tool in symptomatic patients and help to clarify the haemodynamic significance of PV stenosis.[56]

Optimal treatment for PV stenosis is still unknown. Balloon angioplasty alone or in association with stent implantation seems to be efficacious in the acute setting but is also associated with restenosis in 30–50% of the patients.[50] Taken this in mind, prevention of PV stenosis is mandatory and warrants widening the encircling of PVs to include the PV antra. Intense scientific debate is ongoing also on the possibility that different sources of energy, such as cryothermal energy applied through cryoballoon technology, could reduce the risk of PV stenosis. Even though theoretically cryothermal energy should avoid the development of fibrosis and/or stenosis, concern has been raised recently after the publication of the results of the STOP-AF trial, where cryoballoon therapy was associated with a 3.1% incidence of PV stenosis.[57]

Phrenic Nerve Injury

Phrenic nerve injury is another well-described complication of AF ablation. Sacher *et al*.[58] first examined rates of phrenic injury in 3755 consecutive patients who had undergone AF ablation at five different centres between 1997 and 2004. Phrenic nerve injury occurred in 0.48% of cases, with right phrenic nerve affected more frequently then the left. Right phrenic nerve injury usually was associated with the electrical disconnection of the right superior pulmonary vein or of the superior vena cava. Left phrenic nerve injury occurred instead after ablation of the left atrial appendage. Phrenic nerve palsy is usually associated with dyspnea, cough, or hiccups; diagnosis is usually made with evidence of diaphragmatic elevation at the chest X-ray. Prognosis of phrenic nerve injury is usually very good: complete recovery has been described in a report by Bai *et al*.[59] after an average follow-up of about 9 months.

Phrenic nerve injury has been described also consequently to AF catheter ablation with different technologies. For example, in the STOP-AF trial, the incidence of right phrenic nerve palsy was 11.2%

with a complete resolution noted in >80% of the cases.[52] Anecdotal case reports have reported phrenic nerve injury during PVI using the Ablation Frontiers pulmonary vein ablation catheter,[60] during PVI using a novel endoscopic ablation system[61] or during PVI obtained with a forward directed, high-intensity focused ultrasound balloon catheter.[62]

Avoiding this complication can be attempted using 'pace-mapping' with a high output in the areas of presumable contact with phrenic nerves (usually right superior pulmonary vein, superior vena cava, and the roof of left atrial appendage) before delivery of any type of energy. Recently, Horton *et al*.[63] reported a novel method of localization of the phrenic nerve with cardiac computed tomography and found that a distance between the right pericardionephric artery and the right superior pulmonary vein <10 mm expose patients to higher risks of phrenic nerve palsy using balloon-based ablation systems.

Left Atrial Tachyarrhythmias

Left atrial tachycardias or left atrial flutters are the most common 'electrophysiological' complications of AF catheter ablation. Occurring in up to 31% of patients undergoing this procedure,[64] these arrhythmias are often more symptomatic than AF itself because they are often associated with high regular ventricular response. Usually caused by triggered activity originating from the ostia of reconnected PVs or by macroreentry around large functional or anatomical barriers (such as mitral annulus or previously isolated PVs), these tachycardias are strictly connected with the type of AF ablation previously performed. Several studies have confirmed that PVI obtained with an anatomic approach (simple encircling of the PVs without confirmation of electrical isolation) is associated with a higher incidence of atrial tachyarrhythmias compared with a segmental approach (consisting in PVI guided only by circular mapping catheter).[65,66] A possible explanation of this finding is that substrate AF ablation is more often associated with electrical gaps and electrical gaps are often the primary cause of both triggered and/or reentrant tachycardias.[67] Clinical management of these arrhythmias should be, first of all, conservative (rate control or cardioversion are both suitable options), since about one-third breaks spontaneously. For tachycardia persisting long after ablation, a re-do procedure should be performed using one of the available 3D mapping systems.

Conclusions

Even though catheter ablation is a safe treatment for symptomatic drug-refractory AF, complications can still occur with sometimes very unpredictable outcome. Their knowledge is as important as the knowledge of the procedural technique itself because, in this case more than in other clinical contexts, 'prevention is better than cure'. Hopefully, in the next future, as the worldwide experience will increase accordingly to what has been recently demonstrated,[6] their overall incidence will be falling down allowing a better outcome.

Patient safety is the first and most important rule electrophysiologists (especially if young or inexperienced) should know and try to follow in the context of AF ablation. We firmly believe that knowledge of guidelines is helpful and highly recommendable to this aim. Finally and more importantly, do not forget that 'safety of your patient begins in your office and not in the EP lab'.