Review

Risks and Complications of Catheter Ablation of Atrial Fibrillation: How Do We Avoid Them?

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a prevalence of between 2% and 4% in the general population over 60 years old and an increasing incidence with age.[1] Its presence causes a rise in morbidity and mortality rates, due to the increase of embolic risk, and loss of atrial function with a consequent decrease in cardiac performance. Very often AF is associated with disabling symptoms - such as palpitations, exercise intolerance, and fatigue - that can influence the quality of life significantly. In patients affected by persistent or permanent AF with a rapid ventricular response, the persistent high rate may produce a tachycardiomyopathy that can be reversible when sinus rhythm is restored or the ventricular rate is controlled. This arrhythmia is also a significant social financial burden. In the USA, AF causes more hospital admissions than any other arrhythmia, accounting for nearly one million hospital days per year.[2]

The clinical importance and the high cost of AF create a need for effective treatment. Various management strategies are currently employed, including rate control, cardioversion, maintenance of sinus rhythm, and stroke prevention. Pharmacological treatment strategies directed at the prevention of the recurrence of AF are frequently ineffective or have to be withdrawn because of adverse effects, including ventricular proarrhythmia.

Catheter ablation of AF has recently been described as an effective curative treatment overall in patients with paroxysmal and persistent AF and is becoming more widely available. This therapy was first applied by making linear lesions in the right and/or left atrium. However, the treatment of AF with linear lesion ablation, particularly in the right atrium, has been demonstrated to have a poor efficacy.[3] In fact, only 6% - 25% of patients with idiopathic or paroxysmal AF treated with linear right atrial ablation remained free of symptomatic AF in the absence of antiarrhythmic drugs after a follow-up of 6-21 months.[4-7] Studies of linear left atrial ablation had conflicting results. Two studies reported 40%-58% success rates without antiarrhythmic drugs[4,6] but these results were not reproduced in a third study, where none of patients had a successful outcome after treatment.[7] Moreover, linear ablation of AF shows complications, with a magnitude of related risk that is not yet clear in view of the small number of studies available.[3] The most common complication reported with linear ablation in the left and/or right atrium has been pericardial effusion, which occurred in less than 11% of patients. In about 8% of patients treated with linear ablation in the right atrium sinus node dysfunction occurred. Two serious complications restricted to left atrial ablation are cerebral infarction (up to 8%) and pulmonary vein stenosis, the incidence of which is unclear. Symptomatic pulmonary vein stenosis was reported by Robbins et al[8] in 2 of 18 patients (11%) treated with linear right and left atrial ablation but was not observed in any of the published series of patients who underwent linear ablation of AF.

A few years ago, Haïssaguerre et al[9] demonstrated that atrial ectopic beats within the pulmonary veins were responsible for the initiation of AF in most patients. In the past 5 years, various techniques have been proposed to effectively abolish the pulmonary vein firing responsible for initiating and maintaining AF. The first approach was to target the site of the origin of firing within the pulmonary vein directly.[9,10] However, early experience with focal ablation within the pulmonary vein indicated that the recurrence rate was high and the success rate modest, while the procedure was associated with serious complications such as a high incidence of pulmonary vein stenosis.[3,9,10] This complication was observed in up to 42% of patients,[10] with severe pulmonary vein stenosis reported in up to 14%,[19] and the long-term sequelae of even mild or moderate stenosis are unknown.[3]

Recently, different approaches have been developed to electrically confine the triggers to the pulmonary veins (pulmonary vein isolation). The overall success rate (with or without antiarrhythmic drugs) of this procedure is increasing progressively and at present ranges from 51% to 92%.[9-16] However, although the high success rate is very encouraging for a more widespread adoption of this approach, complications such as cardiac tamponade (up to 2%), cerebrovascular accident (up to 5%), pulmonary vein stenosis (ranging from 0% to 36%, depending on the ablative technique used and the method of assessment), coronary embolism (up to 5%), hemopneumothorax (up to 3%), and pericardial effusion (up to 3%) can still be observed.[9-21]

The most serious complications are pulmonary vein stenosis or thromboembolic events.

Animal data have shown that acute pulmonary vein stenosis is the result of denaturation of collagen, which occurs at 65ºC.[22] In contrast, chronic luminal narrowing of the pulmonary vein from extensive radiofrequency ablation was the result of an inflammatory response with progressive intimal proliferation, collagen replacement of necrotic myocardium, endovascular contraction, and proliferation of elastic lamina over the study period of 14 weeks.[23]

The clinical presentation of this complication varies; the pulmonary vein stenosis is frequently asymptomatic, especially when a mild or moderate degree of stenosis is present or a single vein is involved.[21] The symptoms, when present, appear to be largely respiratory in origin, mimicking more common lung diseases (such as asthma, pneumonia, lung cancer, and pulmonary embolism) and can be underrecognized.

Saad et al[21] reported that 18 (5%) of 335 patients treated with pulmonary vein isolation developed severe pulmonary vein stenosis, defined as a luminal narrowing by more than 70%. Forty-eight percent of these patients were asymptomatic. Among the symptomatic patients, shortness of breath was the most frequent symptom (44%), followed by persistent cough (39%), hemoptysis (28%), and pleuritic pain (22%). These symptoms may be explained by the slowly increased intravascular pressure in the pulmonary circulatory system. Vascular resistances in the affected lung segment may be elevated by the reduction or absence of flow through the stenotic pulmonary vein.

Other authors also described drug-refractory pneumonia in patients with pulmonary vein occlusion after ablation. Ernst et al[24] explained these symptoms by a lesser degree of ventilation associated with a less perfused lung segment. These poorly perfused and ventilated segments offer ideal conditions for bronchopulmonary infections.

It seems that symptom severity was not related only to the degree of stenosis but also to the number of stenotic pulmonary veins. Radiographic findings were abnormal in 50% of patients with severe stenosis and were mainly represented by lung consolidation and left pleural effusion (78% and 56% of patients respectively).[21] In the same report symptoms improved spontaneously over time in 50% of patients and were related to improvement in the radiographic abnormalities detected, although other hemodynamic compensatory mechanisms (such as development of collaterals) may also play a role.

Spiral computerized tomography (CT) scan and magnetic resonance imaging of the pulmonary veins can reveal the correct diagnosis and lead to appropriate therapy. However, in the previously cited study[21] pulmonary vein angiography (the diagnostic gold standard) confirmed total venous occlusion in only one of seven patients who had such findings on CT scan. This might have important implications for planning pulmonary vein interventions, considering that in the presence of total occlusion the dilatation procedure is more challenging, if it can be performed at all. Therefore, the sensitivity and specificity of these noninvasive techniques need to be studied further.

Currently, we cannot offer a validated treatment to patients who have developed severe pulmonary vein stenosis. Pulmonary vein balloon angioplasty with stenting is the most widely used interventional strategy[21,22,25] and is recommended in affected patients because lesions can progress to total occlusion, precluding dilatation and potentially resulting in hemodynamic compromise. However, the follow-up after pulmonary vein dilatation showed a high incidence of severe restenosis (47%).[25] Thus, pulmonary vein stenosis is one of the most serious complications after a pulmonary vein ablation procedure, with limited treatment options, and rigorous efforts have been made in the attempt to prevent its occurrence.

Pulmonary vein stenosis can be minimized by delivering the radiofrequency energy at the pulmonary vein-left atrium junction. Haïssaguerre et al[11] reported that the incidence of stenosis (defined as a diameter reduction >50% detected by angiography early after ablation) was 5.5% after a mean follow-up of 8 months. The prevalence of pulmonary vein stenosis was the highest for the left inferior pulmonary vein (7% of left inferior pulmonary veins versus 1.5% of all other pulmonary veins, $p<0.05$) and when the maximum delivered radiofrequency power reached 45 W. With limitation of power to below 30 W at the ostium, the authors did not observe pulmonary vein stenosis during a short-term follow-up. In another study the same authors reported the absence of pulmonary vein stenosis in 70 patients treated with pulmonary vein ostial segmental ablation guided by a circumferential mapping catheter (mean follow-up 4±5 months).[12]

The incidence of pulmonary vein stenosis in a long-term follow-up was evaluated by Arentz et al.[13] Two years after radiofrequency ablation, 9 of 47 patients (19%) followed with transesophageal echocardiography and/or magnetic resonance imaging experienced pulmonary vein stenosis of greater than 50%. A complete pulmonary vein occlusion was observed in 4 (8.5%). However, the ablation was performed within the vein in about 50% of patients. Dividing patients treated with ostial ablation from those ablated within the vein, the incidences of pulmonary vein stenosis were 8% and 45%, respectively. It was interesting to note that in this study the temperature and power setting were almost the same as those suggested by Haïssaguerre et al[11,12] to reduce the risk of pulmonary vein stenosis (55ºC and 30-35 W, respectively).

Purerfellner et al[14] performed the pulmonary vein isolation with circumferential mapping and an angiography-guided approach, using an irrigated-tip catheter for the ablation in an attempt to reduce charring and thrombus formation. However, a luminal narrowing by greater than 20% was observed in 7 (18%) of 37 patients and severe pulmonary vein stenosis was seen in 2 of them (5%). In this series the irrigated-tip catheter did not reduce the risk of pulmonary vein stenosis and the risk of stroke (2.7%) compared with other studies focused on ostial pulmonary vein isolation.

Marrouche et al[19] evaluated the impact of different catheter technologies (4 mm tip, 8 mm tip, and cooled-tip ablation catheters) on the safety and efficacy of ostial pulmonary vein isolation. Even though fewer patients were treated with the 8 mm tip catheter, this technology appeared to be superior to the other two in terms of AF recurrences, fluoroscopy, and procedure time. Although no complications were detected in the group operated on using the 8 mm tip catheter, this group was too small and no significant differences were observed compared with the patients treated with the other two catheters.

Despite the efforts made to better define the pulmonary vein ostia and to perform the ablation outside the vein, this target may be difficult to reach with a simple fluoroscopic landmark because of the complex three-dimensional relationship of the pulmonary veins and the left atrium, and may require integration of data from a variety of different techniques.

Pappone et al[15] proposed an anatomic approach for circumferential pulmonary vein ablation. For this purpose, they used a non-fluoroscopic navigation system (Carto) to perform a real-time, three-dimensional left atrium map. The pulmonary vein ostia were defined by fluoroscopic visualization of the mapping catheter tip entering the cardiac silhouette with a spontaneous decrease in impedance and the appearance of an atrial potential. However, as the same authors described, the definition of the true pulmonary vein ostia may also be difficult with Carto, and they do not rule out that a separate pulmonary vein branch could be missed in some patients.[15] Nevertheless, performing circumferential lines with contiguous focal radiofrequency lesions at a distance of greater than 5 mm from the identified pulmonary vein ostia, they obtained a success rate of 80% after a follow-up of 10 months without pulmonary vein stenosis (on transesophageal echocardiography) or thromboembolic episodes. However, these data were not confirmed in other studies. Kanagaratnam et al,[16] performing the ablation at the ostium of the pulmonary vein (defined using the Carto system and angiography), documented pulmonary vein stenosis with CT scan in 36% of patients (severe and moderate pulmonary vein stenosis were seen in 10% and 19% of patients, respectively). In our experience from 16 patients treated with circumferential pulmonary vein isolation, as previously described,[15] severe pulmonary vein stenosis was observed in 1 patient (6%). Moreover, complete success, defined as the absence of AF recurrences, was observed in only 28% of patients after a follow-up of 7 months.

Recently, Marrouche et al[20] evaluated the effectiveness of intracardiac echocardiography (ICE) to improve the long-term success rate and minimize the complications. Pulmonary vein isolation was performed using circular mapping alone (group 1), circular mapping and ICE (group 2), or circular mapping and ICE with titration of radiofrequency energy directed by visualization of microbubbles with ICE (group 3). The ICE was also used to define the ostium, to ensure a correct circular mapping position and appropriate energy delivery at this site. In patient group 3 ablation was performed with energy delivery titration by monitoring microbubble formation. Two types of bubble pattern were described in this report: scattered microbubbles (type 1), reflecting early tissue overheating, and a brisk shower of dense microbubbles (type 2), reflecting an impending impedance rise. In this group of patients power was titrated upward (5 W increments) until the formation of type 1 bubbles was detected. When this bubble pattern was seen, energy was titrated down by 5 W decrements until microbubble generation subsided. Energy delivery was immediately terminated when type 2 bubbles were seen. In this study ICE-guided pulmonary vein isolation with energy titration was more effective than ICE-guided pulmonary vein isolation with a fixed power setting or angiography-guided circular mapping alone (success rates were 90%, 83%, and 80% respectively after a mean follow-up of 14 months). Moreover, the pulmonary vein isolation under ICE-guided and microbubble energy monitoring decreased the risk of complications compared to the other groups. Severe pulmonary vein stenosis was not observed in this group of patients, but was documented in 3.5% and 1.8% of groups 1 and 2 respectively. Moderate (50%-70%) pulmonary vein stenosis was also less frequent in group 3 compared with groups 1 and 2 (2.5%, 5%, and 4.5% respectively). No cerebrovascular events were detected in group 3, compared with embolic events observed in 3.5% and 3% of groups 1 and 2 respectively. These authors also observed that the pulmonary vein ostium defined angiographically was found to correlate with the ICE-defined pulmonary vein ostium in only 15% of pulmonary veins. In the other 85% of cases ICE showed that placement of circular mapping based on angiography was inaccurate and distal to the true pulmonary vein-left atrium ostium (5±3 mm within the vein).

ICE is also useful to evaluate catheter tip-tissue contact, helping to avoid delivering energy with poor contact between the ablation catheter tip and the endocardial surface, which may result in increased power output, inefficient lesion formation, and increased risk of coagulum formation.[20] Showers of dense microbubbles preceded rises in impedance by 3-5 s, and it has been demonstrated that an increase in impedance is associated with an increased risk of coagulum formation and endothelial and subendothelial layer injury. Therefore, by monitoring the power titration with ICE, preventing type 2 bubbles, it is possible to avoid improper lesion formation, and this could explain the lower occurrence of severe pulmonary vein stenosis observed with this approach. Marrouche et al[20] demonstrated a poor correlation between microbubble formation and delivered energy parameters (power and temperature); type 1 and type 2 bubbles were observed for different power and temperature settings without significant differences in the range of 20-50 W or 20-50°C. On the basis of these data, the low energy setting (<30 W) does not exclude the possibility of improper lesion formation and the risk of pulmonary vein stenosis or cerebrovascular accident. In our electrophysiology lab, 48 patients with symptomatic paroxysmal (20 patients), persistent (21 patients), and permanent AF (7 patients) underwent pulmonary vein and superior vena cava isolation under ICE and circular mapping guide with energy monitoring as previously described. All four pulmonary veins were isolated in every patient. Complete isolation of the superior vena cava was achieved in 44 patients (92%). After a mean follow-up of 6±2.6 months the success rate was 92% (44 patients), with complete success (defined as the absence of AF recurrences in the follow-up without antiarrhythmic drugs) in 69% and partial success (defined as the absence of AF recurrences in the follow-up with previously ineffective antiarrhythmic drugs) in 23% of patients. The radiofrequency energy delivered during the ablation ranged from 30 to 100 W. The procedure was complicated in one case by a cerebrovascular embolic event that occurred in one of the first patients treated with this approach. No severe pulmonary vein stenosis was observed during the procedure or in the follow-up.

Recently Kok et al[26] reported the occurrence of stroke after AF ablation in 3 of 56 (5%) of patients. In this report all 3 patients who developed stroke were more than 60 years old and 2 of them had a prior history of transient ischemic attacks. This percentage is high compared with previous reports in which the incidence of cerebrovascular events, including transient ischemic attacks, was up to 2.7%.[3, 10,11, 13-20] Therefore, the authors hypothesized that the risk of stroke from radiofrequency ablation of AF might be higher in older patients, especially in those with a history of transient ischemic attacks.

A similar observation was made in our series, where a cerebrovascular event was detected in a 74-year-old patient with a previous history of transient ischemic attacks, maintaining activated clotting time (ACT) around 250 s and using two large 8.5 F sheaths in the left atrium. However, in our opinion there are other possible reasons for the high percentage of stroke reported by Kok et al,[26] as follows:

1. The intravenous heparin administration started after successful double trans-septal catheterization with the first sheath, which remained in the left atrium without anticoagulation. Moreover, the ACT was not always maintained above 300 ms in the affected patients (the lowest ACT recorded ranged between 219 and 274 s).
2. The use of two large 8.5 F sheaths instead of 8 F in the left atrium for an extended period of time might promote clot formation despite anticoagulation.

Kok et al[26] performed the ablation under ICE with radial cross-sectional imaging and limited penetration (single frequency of 9 MHz). Therefore, structures distal to the echo catheter (such as the pulmonary vein ostia or catheter-tissue interface) were difficult to detect, and this may explain why bubble formation was not seen in this study. Marrouche et al,[20] using a phased-array ICE with frequency adjustable from 5.5 to 10 MHz, were able to see the more distal structures and the bubble formation at good resolution; no thromboembolic complications were observed in the group of their patients in whom power titration was guided by microbubble formation. In contrast, embolic events were detected when pulmonary vein isolation was performed using circular mapping alone or circular mapping and intracardiac echography without microbubble monitoring (3.5% and 3% of patients, respectively). Continuous ICE monitoring may also be able to visualize char or thrombus formation, allowing adequate countermeasures to be taken.

In conclusion, at present the integration of data from a variety of different technologies (ICE, angiography, fluoroscopy, and circular mapping catheter) seems to be the most effective strategy for avoiding serious complications, such as pulmonary vein stenosis or cerebrovascular events, detected during radiofrequency ablation of AF. The target of the ablation must be the pulmonary vein-left atrium junction, and more distal energy delivery must be carefully avoided. When considering this procedure, caution is advisable in patients suspected of being at increased risk of severe complication (i.e. older patients with a previous history of cerebrovascular events). Aggressive anticoagulation with heparin should be maintained during the procedure.

Alternative sources of energy (ultrasound,[17,18] cryoablation, laser energy) and new catheters (through-the-balloon circumferential ablation technology) have been developed in the attempt to reduce the risk of complications without a decrease in efficacy. However, further studies are needed to demonstrate that these technologies are able to fulfil these goals.

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