REVIEW

Effect of Diabetes Mellitus on Atrial Fibrillation Catheter Ablation Outcomes

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Abstract

Patients with diabetes mellitus commonly are suffering from atrial fibrillation since these two conditions share pathophysiological mechanisms. Catheter ablation of atrial fibrillation is the cornerstone therapy for rhythm control in symptomatic patients with paroxysmal or persistent atrial fibrillation. Data regarding the efficacy and safety of catheter ablation from large randomized clinical trials in this population are limited. The only available data from small clinical trials and meta-analyses have shown a superiority of catheter ablation compared to antiarrhythmic drugs although there are some limitations.

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Key Words: diabetes mellitus; atrial fibrillation; catheter ablation; recurrence

Abbreviations: AAD = antiarrhythmic drug; AF = atrial fibrillation; CA = catheter ablation; DM = diabetes mellitus; PV = pulmonary vein

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population and is related with high risk of thromboembolic events and heart failure. Epidemiological studies have shown a close relationship between diabetes mellitus (DM) and the risk of AF and reported that DM is an independent risk factor for AF. [1] The incidence of AF and atrial flutter in patients with DM has been reported to be 14.9% and 4%, respectively. [1] The inflammation process and the oxidative stress contribute to the pathogenesis of apoptosis and to the formation of advanced glycosylation end products leading to the so-called "diabetic cardiomyopathy''. [2-4] There is evidence that the HbA1c level is associated in a linear manner with the risk of AF in both diabetic and no diabetic patients. [5] Nevertheless, the strict glycemic control in the ACCORD trial has not been correlated with a lower rate of new onset AF in diabetic patients although these had an increased risk of morbidity and mortality compared to the diabetic patients without AF. [6]

As catheter ablation (CA) of AF is considered to be a first line therapy in selected patients with paroxysmal or non-paroxysmal AF, it is also employed increasingly in patients with DM [7]. It should be noted that the increased prevalence of coronary artery disease in patients with AF restricts the use of the most common antiarrhythmic drugs, such as class IA and IC drugs flecainide and propafenone, since they could be potentially harmful due to their proarrhythmic effect. [8,9] Moreover, it should be taken into account that the thromboembolic and bleeding complications are definitely more frequent in patients with DM who undergo percutaneous interventional procedures, such as CA of AF. [10] Despite the large volume of data in the literature regarding the CA results in patients with AF, data concerning patients with DM are limited to small, usually single center non-randomized studies.

Superiority of ablation versus antiarrhythmic drugs for the maintenance or sinus rhythm

Nowadays, rhythm control in patients with AF is achieved either with antiarrhythmic drugs (AADs) or with catheter ablation. Both strategies have been compared in clinical trials and ablation has been shown superior to AADs. One of the first published randomized trials, were designed on this basis, was the A4 study. The reported prevalence of DM in the patients underwent CA or received AADs was 1.9% and 3.4%, respectively, indicating thus that the population of diabetic patients was under-represented. This trial demonstrated the superiority of CA versus AADs, regarding the maintenance of sinus rhythm and quality of life. [11] The largest randomized clinical trial which compared the radiofrequency CA with AADs, as first line treatment, in patients with paroxysmal AF is the MANTRA-PAF study. [12] Although, there was no significant difference during the 2-year follow up period in the intention to treat analysis between the two groups, the recently announced results of the 5-year follow up revealed the superiority of the CA on the rhythm control. [12, 13] In this trial, enrolled patients with DM were only 4% and 7% of the CA and AADs group, respectively. [12] Additionally, in the RAAFT-2 trial, which was a similar design clinical study, only 1.5% and 6.6% of the patients of the CA and AADs group, respectively, suffered from DM. [14]

The cornerstone of AF ablation is the circumferential electrical isolation of pulmonary veins (PVs) in both in patients with paroxysmal and persistent AF, either with radiofrequency or with cryoballoon technology. The optimal sites of deploying the ablation lesions are the ostia of left and right PVs targeting the elimination of PVs potentials. The ''Achilles heel'' of the ablation procedures is the recurrence of AF and the need for redo-procedures, mainly due to electrical reconnection of the PVs or due to

the progress of the AF and the structural remodeling of the left atrium. [7] Especially in patients with DM, the possibility of the presence of atrial fibrosis is higher compared to other patients because of the pathogenetic mechanisms that have been mentioned before, such as the inflammation process. [15,16]

Data concerning the efficacy of catheter ablation in diabetic patients with atrial fibrillation

A study which enrolled patients with paroxysmal and persistent AF who were randomized to undergo CA for AF or to receive AADs showed a significant difference after 12 months follow-up since 42.9% of the patients on the AADs group vs. 80% of the CA group were free from AF (*p=0.001*). [9] A meta-analysis of fifteen randomized and/or observational studies including 1464 patients with DM who underwent CA for symptomatic AF, was recently published. The mean follow-up period was 27 months and the overall long term efficacy in sinus rhythm after CA was 66%. After the first CA procedure about 41-56% of the patients were free of arrhythmia. About 37% of the patients underwent a redo ablation procedure after a mean period of 12 months after the first one. In a meta-regression analysis was performed in order to evaluate the potential correlation of the baseline characteristics and the incidence of the recurrence of AF [17]. The higher basal HbA1c levels, the advanced age and the higher BMI were correlated with a higher AF recurrence rate (*p<0.001*) suggesting a possible pathogenetic mechanism of poor metabolic control. It should be noted, that in this meta-analysis, neither left atrial enlargement nor paroxysmal versus persistent AF were correlated with AF recurrence [5].
Furthermore, data from the German Ablation Registry were collected from 51 centers between 2007 and 2010, comparing the results of CA of AF in patients with DM versus those without DM. Totally 4327 patients (333 with DM and 3994 without DM) were followed up for a median period of 460 days and there were no significant differences concerning major adverse cardiac and cerebrovascular events (*p=0.59%*). Patients with DM had similar percentages of stroke or transient ischemic attack compared to non-diabetic patients (*p=0.49*). Major or moderate bleeding rates were higher in patients with DM during the follow-up period (*p=0.011*). Finally, it should be noted that patients with DM reported a significant increase in functional New York Heart Association (NYHA) class and, on the other hand, patients without DM reported a decrease in NYHA class (DM: 50.9% vs. no-DM: 32.9% NYHA II–IV, *p<0.001*) [18].
As regarding the antidiabetic drug therapy, pioglitazone has been shown to have beneficial effects on CA outcomes. A prospective observational study included 150 consecutive patients with DM who underwent CA and were receiving or not pioglitazone. After a single procedure and a follow-up period of 15 months, 86.3% of the pioglitazone group vs. 70.7% of the control group remained in sinus rhythm without AADs (*p=0.034*). In the multivariate analysis, treatment with pioglitazone as well as renin-angiotensin inhibitor was associated with reduced atrial tachycardias rate. [19]

Conclusion

AF is commonly present in diabetic patients and taking into account that the prevalence of both is going to increase in the near future, more data is required regarding the modern therapeutic approaches, like the catheter ablation. Structural and electrical remodeling as well as inflammation and oxidative processes, seem to play a potent role on the initiation and the maintenance of AF in diabetic patients. A crucial question is whether catheter ablation could be performed in the early stages of the AF, especially in diabetic patients, in order to have maximal beneficial effects. There are ongoing large scale multicenter clinical trials, such as CABANA and EAST trials, which are going to add new data in this field. [20,21] In the daily clinical practice, the results of the ARREST-AF trial, which demonstrated that the aggressive management of the risk factors, such as diabetes and body weight, could improve the long-term success of AF ablation should be taken into account from the physicians. [22]

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