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Catheter Ablation of Atrial Fibrillation in Overweight and Obese Patients

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Abstract

Obesity has reached epidemic proportions, and is associated with increased all-cause mortality. Atrial fibrillation(AF), the most common sustained arrhythmia in the clinical practice, is associated with an increased longterm risk of stroke, heart failure, and all-cause mortality. Accumulating data points out to an indispensable role of inflammation in both obesity and AF. Recent studies have documented an increasing risk of AF with increasing body mass index (BMI). The pathophysiological alterations associated with overweight and obesity lead to atrial stretch and atrial enlargement creating the substrate for AF development. Catheter ablation of AF has been widely accepted as an important therapeutic modality for the treatment of patients with symptomatic,drug-refractory AF. Previous studies assessing the impact of BMI on AF catheter ablation outcomes have given conflicting data. Given that overweight and obesity, as defined by BMI, and AF are closely linked,the present review sought to investigate the impact of BMI on the efficacy and safety of AF catheter ablation.

Introduction

Obesity has reached epidemic proportions, and is associated with increased all-cause mortality .[1]Obesity, a state of chronic low-grade inflammation,
is considered a risk factor for hypertension,stroke, coronary artery disease, diabetes mellitus, left ventricular hypertrophy, left atrial enlargement, ventricular diastolic dysfunction, congestive heart failure, and obstructive sleep apnea(OSA) .[2-4] The body mass index (BMI), which describes relative weight for height, is significantly correlated with total body fat content .[1] This index can be used to assess overweight and obesity. Normal individuals display aBMI of 18.5 to 24.9kg/m2. Individuals with a BMI of 25 to 29.9kg/m2 are considered overweight,
while individuals with a BMI≥30kg/m2 are consideredobese.[1]

AF and Stroke:

Atrial fibrillation (AF), the most common sustained arrhythmia in the clinical practice, is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality. [5-8] Accumulating data points out to an indispensable role of inflammation in the genesis and maintenance of AF .[9-11] Several studies have reported significant associations between high BMI and AF development .[12-18] The pathophysiological alterations associ-

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ated with obesity lead to atrial stretch and atrial enlargement creating the substrate for AF development.[19-22] These data indicate that both obesity and AF are contemporary interlinked epidemics and pose a large public health burden in the future.

Catheter ablation of AF has been widely accepted as an important therapeutic modality for the treatment of patients with symptomatic,drug-refractory AF .[23,24] Ablation strategies which target the pulmonary veins (PVs) and/or the PV antrum (segmental or large circumferential lesions) are the cornerstone of AF ablation procedures, irrespective of the AF type. [23] Catheter ablation of paroxysmal AF aiming at electrical PV isolation (PVI) results in maintenance of sinus rhythm in 60 to 85% of patients .[25,26] On the contrary, PVI is considered insufficient to eliminate persistent or long-standing persistent AF leading to significantly lower success rate of this method. [27]Data on AF catheter ablation outcomes in overweight and obese patients are limited. [25,28-36] Given that overweight and obesity, as defined by BMI, and AF are closely linked, the present review sought to investigate the impact of BMI on the efficacy and safety of catheter ablation of AF.

Obesity and AF Development

Obesity is an ever increasing problem and is associated with an increased incidence of AF. In the Danish Cancer, Diet and Health study ,[12] an increase of one unit of BMI corresponded to an increase in risk of AF of 1.08. Insights from the Canadian trial show that BMI independently predicts AF recurrence .[37]In Women's Health Study,BMI was associated with short- and long-term increaes in AF risk, accounting for a large proportion of incident AF, independently of traditional risk factors.This relationship was linear, with a 4.7% increase in risk of incident AF for each kg/m2increase in BMI.[17]Another study of 6903 Swedish men demonstrated that long-term weight gainfrom 20 years to midlife was associated with anincreased risk of AF.[13] Furthermore, analyses among participants of the Framingham Heart Study and the Framingham Offspring Study showed that obesity was associated with a 50% increase in the risk of AF.[18] A meta-analysis found that obesity increased the risk of developing AF by 49% in the general population and the risk escalated in parallel with increased BMI .

According to the results of another research study,[15] which included 8051 consecutive patients who had undergone cardiac surgery,obesity was an independent predictor of new-onsetAF after the surgery. Similarly, in a study of 5085 patients who underwent isolated coronary artery bypass grafting surgery, obesity was a powerful risk factor for the occurrence of post-operative AF, in patients older than 50 years .[16] In addition,obesity has been also implicated as a risk factor for progression of paroxysmal AF to permanent AF, and is associated with an increased defibrillation threshold in internal cardioversion [38,39]

The electrophysiological mechanisms by which obesity may lead to AF remain to be elucidated. Left atrial enlargement, a recognized precursor of AF, [19] is strongly correlated with increased BMI or adiposity. [20-22] Other factors characterizing obesity that predispose to AF are ventricular remodeling, elevated plasma volume, [40] ventricular diastolic dysfunction ,[41] and enhanced neurohormonal activation .[42] Another potential mechanism by which obesity may lead to the development of AF is OSA.[4]Obesity is closelyrelated with OSA.[43,44] OSA predisposes to a number of arrhythmogenic events, including hypoxia, hyper-capnea ,[45,46]increased sympathetic tone [47-49] and transient atrial dilatation,[50,51] factors that may predispose to AF development. Previous studies have clearly shown an important association between OSA and AF. [52,53] In addition, obesity is considered as a state of chronic low-grade inflammation, and weight loss significantly reduces thelevelsofseveralinflammatoryindexes.[54,55]Overweight and obese patients exhibit increased levels of several conventional markers of infla mation and oxidative stress including WBC count, fibrinogen, uric acid, alanine aminotransferase (ALT), and gamma-glutamyltransferase(GGT).[36] Previous studies have demonstrated the implication of inflammation and oxidative stress in the pathophysiology of AF, although it is not clear yet whether these processes are the cause or the consequence .[56-60] Therefore, it is reasonable to assume that obesity-associated inflammation may contribute to the left atrial remodeling, and therefore to AF development.

AF and Inflammation

The role of inflammation in the genesis and perpetuation of AF is under investigation. Whether initiation of AF activates direct inflammatory effects or whether the presence of a pre-existing systemic inflammatory state promotes AF development remains unclear .[9-11]Both mechanisms may interrelate indicating that inflammation is not only a response to the underlying arrhythmic process but also an integral part of it.[61]Abnormal atrial histology was uniformly found in multiple biopsy specimens in all patients with lone AF,with 66% of them showing evidence of occult myocarditis .[62] Additionally, inflammatory markers have been related to future AF development among patients in sinus rhythm. [9,63] These findings favour the hypothesis that inflammation may act as an initiator rather than as a consequence of AF. On the other hand,,rapid atrial activation has been shown to induce calcium accumulation within the atrial myocytes leading to overload and in some cases to apoptosis that subsequently triggers a low-grade inflammatory response.[57,61,64]

Several inflammatory indices have been related to future AF development, AF persistence, and AF recurrence following electrical cardioversion. [9,11] WBC count is a readily available marker of systemic inflammation. Elevations in WBC count have been implicated in the pathogenesis of AF. A pronounced increase in postoperative WBC count independently predicted the development of postoperative AF. [65,66]A significant decrease of WBC count has been additionally observed in patients with AF following successful electrical restoration of sinus rhythm .[67] Neutrophil accumulation may participate in atrial remodeling by the release of activated substances, including oxygen free radicals, proteases, and pro-inflammatory cytokines. We have previously showed that pre-ablative WBC count is an independent predictor of AF recurrence following PV isolation. A WBC count ≥6280 mm predicted AF recurrence with a sensitivity and specificity of 70.4% and 69.8%, respectively .[68]CRP,a well established marker of systemic inflammation, represents a robust and significant predictor of AF relapse following successful electrical cardioversion.[10,11,69]

Previous studies have shown that CRP levels are related to the left atrial size and AF duration before cardioversion, providing evidence of an association between inflammation and atrial structura remodeling.[70,71] Another established marker of the inflammatory cascade is IL-6. Previous studies have shown increased levels of IL-6 in patients with AF compared with healthy controls .[70] In addition, new biomarkers of inflammation and collagen turnover, such as carboxyl-terminal telopeptide of collagen type I (ICTP), metalloproteinase (MMP)-2, tissue inhibitor of MMP-2 (TIMP-2), atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP) were found elevated in patients who experienced AF recurrence after ablation. [72,73]

The impact of overweight and obesity on the efficacy of AF catheter ablation

Previous studies assessing the impact of overweight and obesity on AF catheter ablation outcomes have given conflicting data. Mainigi et al. have shownthat very late AF recurrence more likely occurs inpatients > 200 lbs .[25] In this study, AF recurrence was defined as recurrence ≥12 months postprocedural. In a prospective study including 109 patients who underwent circumferential PVI, Chilukuri etal. haveshown that BMI is an independent predictor of procedural failure. Each unit increase in BMI was associated with an 11% increase in the probability of recurrent AF. However, in this study, clinical success was defined as atleast 90% reduction in AF burden after a three month "blanking period".[28] Patel et al. have recently demonstrated that higher BMI (>30 kg/m2) predicts procedural failure in a female population who underwent PV antral isolation with or without superior vena cava isolation and complex fractionated atrial electrograms (CFAEs) ablation after a blanking period of 8 weeks .[29] In a recent study including 186 patients with paroxysmal or non-paroxysmal AF who underwent PVI, overweight and obesity were independent predictors of AF recurrence. In this study, AF recurrence was defined as arrhythmia recurrence after a three month "blanking period" .[30]On the contrary, Jongnarangsin et al. reported no association between obesity and freedom from AF recurrence following catheter ablation of CFAEs.[31]However, PVI was not tested in their study. Richter et al. reported similar findings in a study of 234 patients who underwent segmental or

Table 1 Studies addressing the role of overweight and obesity on AF catheter ablation procedural outcomes.

Study	Number of patients	Mean age (years)	AF Type	Ablation strategy	Follow-up period	Main findings
Mainigi et al. [25]	342	54±11	PAF:65% NPAF:35%	Segmental PVI	≥ 12 months	A body weight >200 lbs was associated with very late AFrecurrence (≥12 months).
Chilukuri et al. [28]	109	60±10	PAF:67% NPAF:33%	Circumferential PVI	11±4 months	A BMI ≥30 kg/m2 (obese) was an independent predictor of AF recurrence. In this study, clinical success was defined as at least 90% reduction in AF burden after a three month "blanking period".
Patel et al. [29]	3265 (females)	59±13	PAF:46% NPAF;54%	Circumferential/ antral PVI Superior vena cava isolation CFAEs ablation	40 months	A BMI ≥30 kg/m2 (obese) was associated with AF recurrence after a "blanking period" of 8 weeks.
Cai et al. [30]	186	55±12	PAF:87% NPAF:13%	Circumferential/ antral PVI CFAEs ablation	24 months	A BMI ≥ 25 kg/m2 (Overweight/ obese) was associated with AF recurrence after a three month "blanking period".
Jongnarangin et al. [31]	324	57±11	PAF:72% NPAF:28%	CFAEs ablation	7±4 months	BMI was not predictive of AF recurrence after a two month "blanking period".
Richter et al. [32]	234	57±10	PAF:70% NPAF:30%	Segmental orcircumferential PVI	12.7 months	BMI was not an independent predictor of AF recurrence after a two month "blanking period".
Bitter et al. [33]	75	60±9	PAF:92% NPAF:8%	Cryoballoon PVI	12 months	In univariate analysis, a BMI >30 Kgr/ m2 was associated with AF recurrence. However, BMI was not an independent predictor of arrhythmia recurrence after a three month "blanking period".
Tang et al. [34]	654	57±12	PAF:78% NPAF:22%	Circumferential/ antral PVI	470±323 days	BMI was not predictive of AF recurrence after a three month "blanking period".
Cha et al. [35	523	54±10	PAF:58% NPAF:42%	Segmental or circumferential PVI Linear lesions Cavotricuspid isthmus ablation	12 months	Although not statistically significant, lower procedural success rates were observed in higher BMI groups. However, BMI was not an independent predictor of AF recurrence after a three month "blanking period".
Letsas et al. [36]	226	56±10	PAF:59% NPAF:41%	Wide circumferential PVI	432±306 days	A significant trend towardsa higher recu rence rate wasobserved in subjects classified above the 50th percentile for BMI(26.6±3.5 Kgr/m2). However, BMIwas not predictive of AF relapseafter a three month "blanking period".
Wokhlu et al. [74]	774	56±10	PAF:55% NPAF:45%	Segmental or circumferential PVI Linear lesions Elimination of all non-PV triggers	3.0±1.9 years	BMI was not an independent predictor of AF recurrence after a two month "blanking period".
Miyazaki et al. [75]	474	61 ±10	PAF:100%	Circumferential/ antral PVI Elimination of all non-PV triggers Cavotricuspid isthmus ablation	30±13 months	BMI was not predictive of arrhythmia recurrence after a "blanking period" of 1 month.

PAF: paroxysmal atrial fibrillation; NPAF: persistent/permanent atrial fibrillation; BMI: bodymass index; PVI: pulmonary vein isolation; CFAEs: complex fractionated atrial electrograms.

circumferential PVI.[32] Using cryoballoon ablation, Bitter et al. have shownthat obesity is not associated with AF recurrence.[33] In a large study including 654 consecutive patients who underwent an index circumferential PVI, Tang et al. have demonstrated a significantly higher incidence of AF recurrence in patients with BMI ≥25 kg/m2 compared with those with BMI <25.0 kg/m2 (41.5% vs 31.5%). As a continuous variable, BMI was also significantly higher in the recurrence group than in the no recurrence. However, in multivariate analyses, BMI was not an independent predictor of arrhythmia recurrence .[34] In a similar study including patients that underwent segmental or circumferential PVI along with linear lesions in cases of persistent AF,AF was eliminated in 75%, 72%, and 70% of the lean, overweight, and obese patients, respectively, at 12 months. Similar rates were observed at 24 months. Although not statistically significant,lower procedural success rates were observed in higher BMI groups.[35] Similarly, in our study,[36] AF recurrence rates following catheter ablation were higher,though not significantly,in overweight and obese subjects compared with normal-weight subjects.After a mean follow-up periodof 432.32±306.09 days from the index procedure,AF recurrence rate was 34.9% for normal weight, 46.2% for overweight, and 46.2% for obese patients. A significant trend towards a higher recurrence rate was observed in subjects classified above the 50th percentile for BMI (26.6±3.5 Kgr/m2). However,BMI was not an independent predictor of AFrecurrence.Analogous findings beenreported by other investigators .[74,75] Table 1 summarizes the data of previous studies addressing the impact of BMI on AF catheter ablation outcomes.

AF catheter ablation procedural issues in overweight and obese patients

Concerning procedural issues, Cha et al. haveshown that the amount of radiation exposure for obese patients is nearly 3 times greater than thatfor lean patients. [35] Similarly, Ector et al. have demonstrated that obese patients receive more than twice the effective radiation dose in relation to normal weight patients during AF ablation procedures. In their study, the mean attributable lifetime risk of all-cancer mortality was 0.060%, 0.100%, and 0.149%, for normal weight, overweight, and obese patients, respectively. [76] In our study ,[36] the mean duration of the procedure was significantly longer in obese patients compared to normal BMI subjects, while no differences in the mean fluoroscopy time were observed among BMI groups. We showed that radiation exposure was significantly higher in overweight and obese patients in relation to normal weight patients .[36] Therefore, obesity needs to be considered in the risk-benefit ratio ofAF ablation and should prompt further measuresto reduce radiation exposure. Radiation exposure can be reduced by the use of intracardiac echocardiography and non-fluoroscopic mapping systems[77,78] No significant differences regarding serious complications (death, stroke, pericardial effusion)were observed between normal, overweight, and obese subject undergoing AF catheter ablation in previous studies.[36,76]In a recentstudy, a BMI>30 kg/m2 was associated with more hematomas and pseudoaneurysms in an all-female cohort .[29]

Conclusions

AF catheter ablation is a safe therapeutic modality in overweight and obese patients. A major concern regarding AF ablation procedure in obese patients is the radiation exposure. Although the majority of studies have demonstrated that BMI is not an independent predictor of AF recurrence, patients with higher BMI seem to display a trend towards a higher incidence of arrhythmia relapse. However, most of these studies are significantly heterogeneous with respect to the AF type(paroxysmalvs. persisted) and the ablation strategy used (segmental or circumferential PVI with or without linear lesions and CFAEs elimination). Therefore, we need more studies without the previous limitations in order to validate the true role of BMI on the efficacy and safety of AF catheter ablation. Whether or not modifying BMI improves outcomes of AF catheter ablation deserves also further investigation.

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