THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 3

REVIEW ARTICLE

The Impact of Obesity on Atrial Fibrillation Review: Prevalence, Pathophysiology, and Challenges in Management

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OPEN ACCESS

PUBLISHED
31 March 2025

CITATION
Kichloo, A., Marrufo, I., et al., 2025. The Impact of Obesity on Atrial Fibrillation Review: Prevalence, Pathophysiology, and Challenges in Management. Medical Research Archives, [online] 13(3).
https://doi.org/10.18103/mra.v13i3.6408

DOI
https://doi.org/10.18103/mra.v13i3.6408

ISSN
2375-1924

ABSTRACT

Atrial fibrillation is a growing global health concern due to increasing prevalence and increasing monetary cost on healthcare. Obesity independently contributes to the development of atrial fibrillation through structural, hemodynamic, and electrophysiological changes, necessitating accountability for these changes in atrial fibrillation treatment. With the prevalence of obesity rising as well, and around 18% of atrial fibrillation cases being attributable to obesity, there is a critical need to address obesity in atrial fibrillation. Despite these strong associations, obese patients remain to be underrepresented in atrial fibrillation clinical trials, limiting the applicability of current treatment guidelines to this population. Treatment of atrial fibrillation in obese patients is altered. Rate control strategies such as using beta-blockers and atrioventricular nodal blockers are less effective due to altered cardiac electrophysiology in obese patients. Rhythm control through cardioversion and catheter ablation also shows reduced efficacy, with higher energy thresholds and increased recurrence rates post-ablation. Increased bleeding risks in obese patients complicate drug pharmacokinetics of anticoagulation treatments. Furthermore, the association between obesity and sleep apnea may further increase risk of developing and worsening atrial fibrillations. Patients with atrial fibrillation and sleep apnea had higher incidences of stroke, pulmonary embolism, and more severe coronary artery disease, which were associated with elevated $CHADS_2$ and CHA_2DS_2-VASc scores. Bariatric surgery has shown promise in reducing atrial fibrillation recurrence and improving procedural success. Lifestyle interventions and comprehensive metabolic may also reduce atrial fibrillation burden and improve outcomes in obese patients.

This paper reviews challenges in atrial fibrillation treatment such as rate and rhythm control, anticoagulation, catheter ablation, cardioversion, highlighting the need for tailored therapeutic strategies and further research, particularly on the role of bariatric surgery and lifestyle modifications in atrial fibrillation prevention and treatment in obese populations.

Introduction

Atrial fibrillation is a supraventricular arrhythmia that carries a significantly high rate of cerebrovascular morbidity and mortality. This cardiac arrhythmia is due to abnormal electrical activity within the heart atrium, causing atrial fibrillation. Characteristics of atrial fibrillation include very rapid tachyarrthmias through electric remodeling, fibrosis, and autonomic neural remodeling.[1–3] Fibrosis and autonomic neural remodeling are known to contribute to positive-feedback loops which promotes atrial fibrillation persistence and recurrence.[2] Risk of developing atrial fibrillation is associated with increased age and comorbidities such as diabetes, high blood pressure, and other heart disease.[4] People with atrial fibrillation are at heightened risk of thrombosis, increasing the risk of stroke, coronary heart disease, peripheral artery disease, cognitive impairment, and physical disability.[5]

Obesity is characterized by excessive body fat accumulation, with BMI of 30 or higher being considered obese.[6] However, BMI does not fully encompass all aspects of obesity. Waist circumference, Waist-to-Hip Ratio, and body fat percentage provide a more comprehensive definition of obesity in patients.[7–9] Obesity if associated with a wide range of health complications including cardiovascular disease, type 2 diabetes, sleep apnea, and certain cancers.[10] Additionally, obesity is also associated with atrial fibrillation development and worsening outcomes.[11] Obesity contributes to atrial fibrillation development through multiple mechanisms, including structural and electrical remodeling of the heart, systemic inflammation, and metabolic dysfunction.[12,13]

Despite this clear link between obesity and atrial fibrillation, obese patients remain underrepresented in major clinical trials investigating atrial fibrillation management, limiting generalizability of current treatment strategies to this population. Limited clinical trial research on obesity often overlooks the inclusion of related conditions, such as obstructive sleep apnea (obstructive sleep apnea), which should be considered in predictive scores for complications associated with atrial fibrillation. With scores such as $CHADS_2$ and CHA_2DS_2-VASc scores being used to assess risk of stroke in patients with atrial fibrillation and guiding decisions of anticoagulation, it is also concerning that these scores lack factors such as obstructive sleep apnea.[14] As a result, this lack of regard may be related to the 5-fold increase in cerebrovascular accidents incurred by patients with atrial fibrillation.[15]

This paper examines the multifaceted impact of obesity on atrial fibrillation-from its pathophysiology to challenges in treatment-and discusses prevalence, promising interventions, other conditions to be considered, and economic implications.

Prevalence of atrial fibrillation, obesity and atrial fibrillation in obesity

Prevalence of atrial fibrillation in the general population has been noted to be increasing due to factors such as an increased average life expectancy, improved post myocardial infarction mortality due to goal directed medical therapy, and increased prevalence of risk factors for atrial fibrillation.[16] According to the Global Burden of Disease study conducted in 2010, the worldwide age adjusted prevalence of atrial fibrillation was 5.96 per 1000 in men and 3.73 per 1000 in women, affecting 33 million people globally.[17] The prevalence of atrial fibrillation in the US is noted to be about 3% across the general population, affecting around 3-5 million people, and is projected to affect 8 million people by the year 2050.[17]

Similarly, obesity is a complex multifactorial disease that has doubled in prevalence across all genders, ages, and geographic locations.[18] An observational study by Chooi et al. noted that globally a total of 1.9 billion and 609 million adults were considered overweight and obese in 2015, representing approximately 39% of the world population. In the American population, the study observed a significant rise in obesity prevalence, increasing from 12.9% in 1980 to 28.3% in 2015. Additionally, the prevalence of those considered overweight in America increased from 45.3% in 1980 to 64.2% in 2015. The relationship between obesity and cardiovascular disease has been investigated and linked to the development of atherosclerosis, symptomatic heart failure, dyslipidemia, type 2 diabetes, and atrial fibrillation.[19] Consequently, it has also been reported that obesity is an independent risk factor for the development of atrial fibrillation ; independent of whether the patient has sleep apnea as well.[20] According to the Atherosclerosis Risk in Communities study done by Huxley et al., it was found almost 1 in 5 cases of atrial fibrillation are attributable to overweight or obesity, compromising approximately 17.9% of all atrial fibrillation cases.[21]

Pathophysiology of atrial fibrillation in obesity, or what are the factors in obesity that trigger atrial fibrillation

Obesity accompanies various hemodynamic alterations which predisposes patients to changes in cardiac morphology that can impact cardiac function.[20] Left atrial enlargement, a well-known predisposing factor to the development of atrial fibrillation, has been noted to have variable prevalence in overweight and obese patients.[22] Due to excessive adipose accumulation leading to increased body mass, Obese patients tend to have increased blood volume which leads to a greater cardiac output, decreased systemic vascular resistance, and no consequent changes in heart rate. As a result, cardiac output increases due to increased left ventricular stroke volume which leads to cardiac remodeling and the development of left ventricular hypertrophy. The development of left ventricular hypertrophy in the setting of obesity is further encouraged by the abnormal function of neurohormonal regulatory systems such as the renin angiotensin aldosterone pathway, increased sympathetic nervous system drive, and even possible lipotoxicity. Progression of left ventricular hypertrophy can lead to left ventricular diastolic dysfunction and even left ventricular failure, consequently causing increased filling pressures to be present in the left atrium causing left atrial dilatation.[20] Comorbidities such as hypertension, diabetes, congestive heart failure, and obstructive sleep apnea all carry the risk of causing left ventricular remodeling and the development of left ventricular

dysfunction through a variety of neural, hormonal, and structural pathways which can subsequently lead to Left atrial dilatation and increased risk of development of atrial fibrillation.[23]

The relationship between epicardial adipose tissue, the neuro-hormonal axis, and inflammatory cytokines has also been associated with electrophysiologic remodeling of the left atrium and is thought to contribute to the development of atrial fibrillation. Prior studies using obese ovine models have demonstrated that increased epicardial fat was linked to adipocyte infiltration into the posterior wall of the left atrial myocardium compared to non-obese control ovine models.[24] Prior studies have demonstrated that adipocyte infiltration into the atrial myocardium disrupts electrophysiologic circuits in place via secretion of Adipokine Activin A (TGF-beta superfamily hormone), Matrix metalloproteinases 2 and 7, and over expression of TGF Beta 1 leading to atrial fibrosis causing conduction slowing, and predisposing a patient to develop atrial fibrillation epicardial adipose tissue has also been shown to secrete inflammatory cytokines such as CRP, IL-6, TNF alpha, and IL-8 which can function as arrhythmogenic substrates when acting upon nearby myocardium.[25,26] Lastly, it has also been described that epicardial adipose tissue houses the ganglion plexus of the autonomic nervous system. Activation of both parasympathetic and sympathetic pathways through epicardial adipose tissue can influence action potential duration and serve as an origin point for a potential trigger to atrial fibrillation.[26] A prior study by Pokushalov et al. demonstrated botulinum toxin injection into epicardial fat pads during coronary artery bypass graft provided substantial atrial tachyarrhythmia suppression both early as well as during 1-year follow-up, without any serious adverse events.[27]

Under representation of obese patient population in atrial fibrillation trials

Underrepresentation of obese patients in trials involving the study of atrial fibrillation remains a great concern despite the increasing global prevalence of obesity and its known relation to the risk of developing atrial fibrillation. Prior studies have demonstrated risk of atrial fibrillation recurrence after ablation or cardioversion is strongly associated with overall increased BMI.[28] Despite this, various randomized control trials assessing catheter ablation versus antiarrhythmic therapy in the setting of atrial fibrillation have been (or are being) conducted which do not stratify their inclusion criteria based on BMI or with the concern for obesity to function as a confounding variable. The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial is an ongoing study which is testing whether the strategy of percutaneous left atrial catheter ablation for the purpose of eliminating atrial fibrillation is superior or not to state of the art pharmacologic therapy.[29] The study is projected to have a 90% power in detecting a 30% relative reduction in total mortality, however, its inclusion criteria do not mention any stratification of BMI and the study design does not control for obesity. Similarly, a prior study by Wilber et al. compared antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation but did not consider patient BMI when matching characteristics of patients.[30] Likewise, a study by Dibiase et al. looked at whether catheter ablation is superior to amiodarone for the treatment of atrial fibrillation in heart failure, however, patients were randomized and matched without any BMI stratification.[31] A meta-analysis by Azad et al. examined 18 similar articles analyzing the effectiveness of catheter ablation versus medical therapy, however, these studies did not stratify or consider the BMI of the patient being treated as well.[32] When evaluating long term outcomes such as recurrence of atrial fibrillation post ablation, concerns must also be raised for an observation known as the Obesity "Paradox" which suggests that obese patients have a significant reduction in all-cause mortality. The cause of this paradox is unclear and could stem from Confounder and Collider bias as well.[33] As a result, results and findings of previous studies may be overly favorable and potentially misleading, as they might not accurately reflect the true outcomes if BMI were properly stratified and represented.

Challenges in heart rate control in obese patients

As mentioned previously, obesity in the setting of atrial fibrillation is associated with a transformation of epicardial adipose tissue which can cause myocardial fibrosis, and microvascular dysfunction through the secretion of proinflammatory mediators.[34] The resulting fibrotic myocardium and inflamed epicardial fat alters the electrophysiological environment of the atrium and adjacent myocardium and can impact the success of rate or rhythm control strategies implemented.[35] Prevention of tachy-arrhythmic cardiac injury is one of the major reasons why rate control strategies such as beta-blockers and atrioventricular nodal blocking agents are used. However, prior studies have put this topic into dispute. A prior study by Mulder et al. conducted a post hoc analysis on the efficacy of rate control in permanent atrial fibrillation II which found that achieving a lower target heart rate of <80 beats per minute did not provide a beneficial outcome and improve overall prognosis.[36] Additionally, a prior study by Qureshi et al. conducted a systematic review and meta-analysis of the use of atrioventricular nodal blocker digoxin in atrial fibrillation, finding an increased risk of all-cause and cardiovascular mortalities, particularly in patients with atrial fibrillation and without heart failure.[37] Furthermore, in patients with fibrotic myocardium, such as those with obesity, the use of beta blockers carries an increased risk of bradyarrhythmia, as achieving a target heart rate often requires dosage up titration.[38] This is supported by prior studies showing that obese patients undergoing rate control strategies are more likely to have higher uncontrolled heart rates compared to those with a leaner body mass.[39] Given these findings, implementing a rate control strategy in obese patients can be particularly challenging and may require further research to identify the optimal treatment approach.

Challenges in rhythm control in obese patients

Similarly, achieving success with rhythm control strategies, such as chemical or electrical cardioversion and catheter ablation, has proven equally challenging in the context of

obesity and atrial fibrillation. Prior studies have demonstrated that patients with a greater body weight tend to have a lower rate of success with cardioversion.[40] This is believed to occur due to an increased threshold of joules required for the electrical energy to effectively reach the atrial environment and achieve successful cardioversion.[11] Indeed, previous studies have shown a higher success rate of cardioversion in obese patients when the initial shock is delivered at higher energy levels.[41] When electrical cardioversion is unsuccessful, chemical cardioversion using various antiarrhythmic medications is often considered. However, these treatments may also be less effective in patients with atrial fibrillation. It is well known that obesity can alter the pharmacokinetics and pharmacodynamics of drug therapy. Medications such as amiodarone have high lipophilicity and tend to have decreased clearance in overweight individuals, however, there are currently no dosage recommendations for obese patients.[42] Additionally, prior studies have also demonstrated an increased atrial fibrillation recurrence rate in obese patients treated with sodium channel blocker antiarrythmic drug therapy compared to non-obese patients.[43] A study by McCauley et al. examined the electrophysiological environment of mice atria in a diet induced obese (DIO) mouse model. It was noted that mice in the DIO group had significant downregulation of *I(Na)* and *I(Ca)* channels compared to normal mice, implying that class 1 antiarrhythmic drugs such as propafenone and flecainide may not be as effective in the treatment of atrial fibrillation in an obese patient.[44] Catheter ablation is another common rhythm control used for atrial fibrillation, however, previous studies have also shown that higher BMI has been associated with higher atrial fibrillation recurrence even after successful catheter ablation.[45] Studies have also shown that catheter ablation complication rate is significantly higher in morbidly obese patients (BMI >40 kg/m2) with a 5% increase noted per 1 U of BMI increase.[46] The challenges in maintaining normal sinus rhythm after catheter ablation in obese patients are likely due to increase myocardial fibrosis and higher levels of epicardial adipose tissue, both of which can reduce the success of ablation procedures.[47,48] Bariatric surgery, which has been shown to decrease epicardial fat volume, can increase the success (decrease atrial fibrillation recurrence) of ablation procedures in obese patients.[49] While various rhythm control strategies are available, their overall efficacy and optimal implementation in managing atrial fibrillation in the context of obesity may require further investigation.

Challenges in anticoagulating obese patients

Patients with atrial fibrillation are at a 5 times greater risk of suffering a cerebrovascular accident.[15] Cerebrovascular accidents have a wide array of outcomes depending on a variety of factors. Presence of atrial fibrillation is linked with an increased mortality in patients with stroke, highlighting the necessity of anticoagulation therapy in this population.[50] Multiple studies have found stroke risk remains consistent across BMI groups, though this is limited by the fact that the highest BMI category studied is BMI >30.[51] Very limited data is also available for outcomes in patients with BMI > 40. Given that obesity is a significant risk factor for atrial fibrillation, patients who would need anticoagulation long term are more likely to fall into even higher BMI groups than the ones studied.

Challenges in catheter ablation in obese patients, recurrence in obese vs non-obese

Atrial fibrillation is commonly triggered by ectopic pulmonary venous foci. Catheter ablation involves radiofrequency energy to electrically isolate the pulmonary veins from the left atrium.[52]

It has been hypothesized that atrial fibrillation recurrence rates for obese patient may be higher than for those with normal BMI. Earlier data regarding recurrence after catheter ablation has shown conflicting results. Some randomized controlled trials show increased recurrence rates for BMI < 30, with others show no significant difference between BMI classes.[53] However, recent prospective studies have shown that BMI > 35 is associated with increased recurrence of atrial fibrillation post catheter ablation.[54]

Pooled data from ~14,000 patients undergoing radiofrequency catheter ablation also points to increased duration of procedure as well as amount of radiation exposure. The risk of post-procedural complications however remains clinically insignificant in the various BMI groups.[55]

Challenges in cardioversion in obese patient population

Atrial fibrillation is converted to sinus rhythm to achieve symptom relief. A safe, effective and reliable method to achieve this is electrical cardioversion. The success of this procedure depends on a multitude of factors. Obese patients have greater chest circumference, higher volumes of pericardial fat, intrathoracic fat, and visceral adipose tissue.[56] These factors specifically lead to higher transthoracic impedance, greater interelectrode distance, and decreased transthoracic current flow, negatively impacting success rates.[40] This has led to exploration of more invasive therapies for these patients. Alternative strategies to enhance cardioversion success rates in obese patients include using 360J instead of 200J, applying manual pressure on adhesive patches with gloved hands, and using paddles instead of patches-all of which have been linked to improved outcomes.[11]

Association between obesity and obstructive sleep apnea

Obesity, obstructive sleep apnea obstructive sleep apnea, type 2 diabetes mellitus are interconnected. One key mechanism involves excess fat accumulation in the neck, tongue, and pharyngeal tissues, which can obstruct the upper airway, leading to apnea or hypopnea. This is especially the case when lying in a recumbent position and during rapid eye movement phase of sleep, due to the generalized loss of muscle tone and decreased muscular effort to open the airway.[57,58] By causing intermittent hypoxia, obstructive sleep apnea induces insulin resistance, which can lead to diabetes and obesity. Through this, a vicious cycle between obesity and obstructive sleep apnea can be seen.[59] Furthermore, a prospective study demonstrated that amongst a population of 349 patients who had roux-en-y gastric

bypass done for clinically significant obesity, 83% of them had undiagnosed obstructive sleep apnea.[60] The similarities between obesity and obstructive sleep apnea are not limited to mechanistic, they also cause comparable adverse cardiovascular, metabolic, and neurocognitive effects.[61]

Is obesity an indirect indicator of $CHADS_2$ score or CHA_2DS_2-VASc score?

Both $CHADS_2$ and CHA_2DS_2-VASc scores are used to estimate the incidence of stroke, pulmonary embolism, and coronary artery disease severity.[62,63] A recently published trial with a prospective data collection and retrospective analysis evaluated 2715 patients that were undergoing atrial fibrillation ablation procedures. The results demonstrated that with increasing body mass index, the incidence of obstructive sleep apnea, hypertension, and diabetes also increases. Consequently, both $CHADS_2$ and CHA_2DS_2-VASc scores increased.[45] Furthermore, an observational study on 254 atrial fibrillation patients were evaluated for comorbidities and complications. This study illustrated that the mean value of both scores increase with worsening obstructive sleep apnea severity as determined by the apnea-hypopnea index.[64] Moreover, sleep-disordered breathing, such as obstructive sleep apnea, is an indicator of higher all-cause mortality and recurrent vascular events in patients with previous strokes.[65] Due to its risk for stroke, proposals have been made to add obstructive sleep apnea into the $CHADS_2$ score, but there is currently not enough evidence.[64,66]

Bariatric surgery and its impact on atrial fibrillation

Multiple retrospective and prospective cohort studies have demonstrated that bariatric surgery is associated with a significantly reduced risk of developing atrial fibrillation, both new onset and post-ablation recurrence.[49,67–73] However, one cohort study illustrates an increased risk of emergency room visit or hospitalization for atrial fibrillation episodes during the first two years after bariatric surgery.[70] Recently, three large sample size cohort trials with greater than five-year follow-up duration demonstrated decreased incidence rate and increase resolution rate of atrial fibrillation.[67,74,75] Of note, there have been no randomized controlled trials on this subject to date.

Should we advocate lifestyle changes or bariatric surgery?

There is limited data that compares weight loss methods, such as lifestyle changes or bariatric surgery. A randomized controlled trial demonstrated that a comprehensive metabolic risk factor management program significantly decreases atrial fibrillation symptom burden and severity, as compared to general lifestyle advice.[76] However, there are no randomized controlled trials comparing bariatric surgery versus an intensive weight loss program or lifestyle advice. Based on cohort studies described above, we recommend bariatric surgery in patients at high risk for developing new onset or recurrent atrial fibrillation. This statement should be evaluated by further randomized controlled trials as aforementioned.

Impact of obesity and atrial fibrillation on healthcare cost

In 2008, obesity accounted for a significant percentage of the total United States healthcare expenditure, almost 5-10%. Each overweight or obese individual in the United States during 2008 spent an average of $1,723 on healthcare.[77] Only two years later, this number increased to $2,646 for obese males and $4,879 for obese females.[78] By 2030, the United States is projected to spend a staggering total of $66 billion on medical costs for obesity.[79] Additionally, due to the associated comorbidities, individuals with obesity are likely to pay higher premiums for healthcare insurance.[80]

From 2001 to 2012, a large registry-based study performed a cost-of-illness analysis for atrial fibrillation patients in Denmark. The study indicated that the average 3-year societal costs per patient for atrial fibrillation ranged from €20,403 to €26,544. The atrial fibrillation -related healthcare costs were 1.3-1.7% of the total healthcare costs.[81] Finally, the atrial fibrillation patients who experienced strokes incur significantly increased healthcare costs due to the hospital admission cost.[81,82]

Conclusion

The increasing global prevalence of obesity has significant consequences on both atrial fibrillation treatment success in patients and monetary costs to healthcare. Obesity contributes to atrial fibrillation development and recurrent atrial fibrillation through various pathophysiological mechanisms, including structural and electrophysiological remodeling of the atrium, increased inflammation, and neurohormonal activations. Despite its strong association with atrial fibrillation, obesity remains underrepresented in clinical trials assessing atrial fibrillation management, leading to potential gaps in treatment strategies.

Addressing these challenges requires further research into optimized anticoagulation, rate and rhythm control, and procedural interventions tailored to obese patients. Bariatric surgery and comprehensive metabolic treatment plans may be a viable option for treating recurrent atrial fibrillation, however, more research is needed to fully assess their effectiveness and long-term benefits.

Conflicts of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

None

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