



Cardiac Strain Biomarkers And Risk Stratification Of Af In Obese Patient

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ABSTRACT: Atrial fibrillation, or AF, is a frequent cardiac rhythm instability, particularly prevalent in the elderly population, with a global impact on millions. Existing treatments for AF face challenges such as limited efficacy and recurrence. Obesity significantly increases the risk of AF and associated cardiovascular complications, influenced by factors such as hypertension, diabetes, and sleep apnea. Understanding the pathophysiological links between obesity and Atrial fibrillation, including oxidative stress, fibrosis, and inflammation, is crucial. Biomarkers such as greater sensitivity troponin, C-reactive protein (CRP), natriuretic peptides (BNP, NT-proBNP), and microRNAs (miRNAs) play a crucial part in predicting also managing AF, particularly in obese patients. These biomarkers offer insights into myocardial stress and remodelling, aiding in early risk stratification and personalized treatment strategies. Current evidence suggests that elevated levels of NT-proBNP and hs-TnT are significant predictors of adverse outcomes in AF patients, emphasizing the need for aggressive management in high-risk groups. Incorporating biomarkers into AF management protocols can enhance the precision of treatment decisions, potentially reducing morbidity and mortality. Lifestyle modifications, rhythm control, antiarrhythmic drugs, and anti-inflammatory treatments are critical in managing AF in obese patients. Further research is essential to optimize the use of cardiac strain biomarkers in clinical settings, advancing towards more effective and individualized approaches for preventing and managing AF in obese populations.

Keywords: Atrial Fibrillation (AF), Obesity, Biomarkers, Risk Stratification, Inflammation.

1. INTRODUCTION:

Frequently sustained heart arrhythmias like AF are associated with considerable Hospitalization and fatality rates, with existing treatments facing challenges such as limited efficacy, high potential for side effects from antiarrhythmic drugs, recurrence, and potential complexities in AF ablation ^[1]. AF is more common in older individuals. While the overall population prevalence is about 2%, it rises to 10-12% among those over 80. This arrhythmia becomes increasingly common with advancing age, making it the most prevalent cardiac rhythm disorder. Based on Global Burden of Disease estimates, AF may impact about 33.5 million

individuals globally, with a prevalence rates varying between 2.5% and 3.5% in various nations [2]. AF is related to certain traditional cardiovascular risk factors, including male sex also advanced age. Modifiable risk variables include coronary artery disease, high BP ,as well as elevated BMI. BMI is calculated by dividing body mass by kg/m². The categories for BMI are: normal (18.5–24.9), overweight (25–29.9), and obese (over 30). In 1988, a brief set of surgical cases first indicated that obesity might predict cardiac perioperative AF, leading to further research on the topic [3]. Patients who are obese or overweight have a greater risk of developing new cardiovascular problems because of their elevated levels of risk factors and inadequate treatment management. Obesity is linked to various cardiovascular risk factors, such as dyslipidemia, type 2 diabetes, and hypertension. Additionally, growing evidence suggests that these risk variables often bunch together in obesity individuals and may collectively elevate their risk of cardiovascular disease [4]. Biomarkers play a crucial l role in prognosis moreover risk assessment for numerous cardiovascular illnesses [6].

To estimate future cardiac risk, we include indicators of high-sensitivity troponin, C-reactive protein (CRP), natriuretic peptides (BNP and NT-proBNP), and microRNAs (miRNAs) In this article, especially in obese patients with AF.

OBESITY AND AF:

Remodeling and size of the left atrium are key predictors of AF in individuals who are obese, even though some research studies have shown significant variations in left atrial size between non-obese and obese

individuals^[37]. A high-calorie diet increased weight for eight months, gradually changing the atrium's electrical and structural makeup^[7]. These included myocardial lipidosis, increased interstitial fibrosis, conduction slowness, and increased conduction heterogeneity. Even when atrial refractoriness remained intact, these variables exacerbated spontaneous and induced AF^[7]. Histological examination showed that epicardial fat had infiltrated the adjacent atrial myocardium. Elevated LA pressure, insufficient LA stretching, slowing of conduction in the PV ostia, decreased productive refractory periods in the atria and PVs, and other electrophysiological abnormalities are seen within obese individuals along with AF^[7] (figure-1).



Figure 1: Pathophysiology of obesity in AF [5].

Mechanisms linking obesity to AF development:

Pro- and anti-inflammatory adipokines, found in large quantities in fat tissue, play an essential part in the emergence of obesity-related comorbidities. It possesses complicated endocrine functions^[7]. Several processes can explain the connection between AF and fat. Inflammation, pericardial fat, and impaired diastolic function have all been identified as key components of the obesity-related AF mechanism^[10].

Additionally, various pro-fibrotic and pro-inflammatory chemicals secreted by adipose tissue can aid in the quick remodelling of the left atrium's anatomy and function and the emergence and perpetuation of electrical conduction abnormalities. Additionally, oxidative stress from adipose tissue and activated autonomic neurons in the ganglion plexus impact the development of AF^[9]. In patients undergoing AF ablation, magnetic resonance imaging has shown that obese groups have longer left atrial and pulmonary vein effective refractory times, increased left atrial pressure, and larger atrial and measured pericardial fat. The degree of heart fat was linked to the recurrence of AF following ablation and its severity. Contiguous atria may experience an arrhythmogenic influence from nearby fat depots^[10].

The remodelling process has also been linked to inflammation and the fibrosis that results from it. In the atria of AF patients, significant scar regions have been found through electro-anatomical tests. In AF patients, the atrial scar has been studied and quantified using magnetic resonance imaging in more recent times. It has been proposed that scar burden and ablation success are related. It has been suggested that severely scarred substrates are sicker and less responsive to rhythm control techniques. In addition to having a strong correlation with obesity, leptin and its related biomarker adiponectin have also recently been linked to AF^[10].

2. IMPORTANCE OF RISK STRATIFICATION IN AF:

AF, the arrhythmia that occurs most frequently in clinical practice is linked to higher amounts of fat. It is thought to be the cause of a 50% rise in AF incidence. Although the pathophysiological connections between AF and overweight are not entirely recognized, multiple factors are significant, including Ventricular adaptation, epicardial adipose tissue, and clinical correlations such as Hypertension, Obstructive sleep apnea syndrome, Type 2 diabetes mellitus, and coronary artery disease (Table-1)^[7].

Risk factor	Pathophysiological alterations
Hypertension	• Remodelling the atrial structure. • reduced diastolic function on the left. • Activation of RAAS. • Slowing conduction.
Type 2 Diabetes mellitus	• Atrial structure remodelling. • Advanced glycation end-product synthesis. • Increased left ventricular mass and wall thickness on ECG.
Sleep apnea syndrome	• Irregular hypoxia during the night. • Carbon dioxide retention. • Sympathetic activation.
Coronary artery disease	• Blocking and slowing down conduction. • Abnormal management of calcium. • Atrial structural remodelling. • Left ventricular failure. • Inflammation and oxidative stress.

Table 1: Risk factors and pathophysiological alterations in obese patients with ^[28,34].

Early and accurate risk stratification will help the doctor develop a timely treatment plan suited to the severity of the patient's condition. However, the current guidelines for management from the Heart Rhythm Society (HRS), the American Heart Association (AHA), the European Society of Cardiology (ESC) 2016 guidelines, and the American College of Cardiology Foundation (ACA) 2014 guidelines do not specifically address Emergency department (ED) treatment and disposition^[15]. Created two distinct prediction models: the AFFORD score (Atrial Fibrillation and Flutter Outcomes & Risk Determination) ^[16].

The Risk Estimator Decision Aid for Atrial Fibrillation (RED AF) score is utilized to predict the probability of adverse outcomes within 30 days after a patient with AF arrives at the emergency room ^[17]. The 30-day all-cause death rate was intended to be predicted by the Atrial Fibrillation in the Emergency Room (AFTER) score. There are two variants available: AFTER, which is more practical, and TrOPs-BAC, which is more complex^[18].

Risk prediction in obese patients:

There's an extensive amount of evidence showing the connection between AF and fat. . The literature currently available indicates that indicates those who are obese have a nearly 50% higher chance of developing Atrial fibrillation when in contrast to lean patients^[7]. In comparison to healthy persons, obese individuals seem to have higher resistance levels, and this increase is correlated with BMI. Furthermore, it was found that compared to controls, individuals with paroxysmal and chronic AF had higher levels of resistance^[19]. Increased lean body mass, body fat percentage, and body fat mass, as well as Anthropometric factors such as weight, height, and BMI, hip and waist circumferences are, are linked to an increased risk of AF ^[20].

3. ROLE OF CARDIAC STRAIN BIOMARKERS:

Cardiac Strain Biomarkers: The first guidelines for managing AF that addressed using biomarkers in AF managing were developed by the European Society of Cardiology in collaboration with EACTS in 2016. For AF patients, biomarkers were suggested as class IIb with a level of evidence B to further reduce the risk of bleeding and stroke. Biomarkers are extremely important in predicting risk and prognosis values for certain cardiovascular diseases. Through their paracrine influence, several factors, including growth factors, the renin-angiotensin system, oxidative stress, inflammation, ion-channel dysfunction, and even adipose tissue, contribute significantly to the development of AF and alter its histology and electrical properties ^[6].

a. Cardiac Troponin Intracellular calcium regulates cardiac troponins and is required for the coupling of myocardial contractions. The three cardiac troponins are heart troponin I, heart troponin T, and heart troponin C. These proteins are fundamental parts of the structural proteins that function in the heart to let actin- and myosin-thin filaments slide past one another. Troponin T and I have far higher sensitivity

and specific for cardiac injury as opposed to troponin C. Any identification of these proteins in the peripheral circulation is always suggestive of heart injury. Despite their differences, TnT and TnI appear to have similar predictive and diagnostic sensitivity and specificity. With the ability to measure high-sensitive troponin, a progressive slowing of cardiac disease may lead to a steady rise in troponin levels. More details regarding troponin's usefulness for the clinical therapy of AF may be beneficial in predicting the risk of future episodes of AF^[6].

b. Cardiac natriuretic peptides: Natriuretic peptides have been studied for some time to learn more about the roles they play in several physiologically important activities^[25]. Atrial NP and B-type NP are two natriuretic peptide (NP) hormones that are secreted in a controlled manner by atrial (appendage) cardiomyocytes with a dual contractile–secretory character^[26]. The atrial natriuretic peptide is mostly generated in reaction to changes in the body's electrolyte and water concentrations as well as to strain on the atrial wall brought on by an increase in volume^[25]. Angiotensin-aldosterone system (RAAS) antagonist, blood pressure control, and natriuresis are only a few of the physiological consequences of the cardiac peptide atrial natriuretic peptide (ANP)^[25]. The protease corin cleaves pre-proANP, which is generated in the atria, to yield the mature 28 amino acid ANP. The second messenger cGMP and the guanylyl cyclase receptor are the two channels by which the downstream signalling pathway of ANP operates^[25]. The primary inducer of cardiac NT myocardial stretch is pressure or volume overload, which causes pro-BNP secretion. Higher levels of BNP and NT-proBNP are typically connected to ventricular malfunction. Heart failure can be diagnosed and treated with the use of NT-proBNP and BNP, two types of natriuretic peptides. Just like troponin, they are also linked to the development of AF, AF during surgery, and the prognosis of AF. Furthermore, the diagnosis of heart failure linked to AF and prognosis of the condition's response to direct current cardioversion have been interrelated with NT-proBNP and BNP. A higher frequency of AF is connected with increased BNP and NT-proBNP levels^[26].

c. C-Reactive Protein (CRP): When the liver is stimulated by various factors, such as interleukins like interleukin 6 (IL-6), which are triggered by inflammation, it Acute-phase protein, C-reactive protein (CRP). Interleukin 6 and CRP, two reliable and well-established markers of inflammation, have been the focus of most studies regarding cardiovascular diseases and AF^[21]. Indications of inflammation, such as oxidative damage, leukocyte infiltrations, and fibrosis, have been observed in samples of atrial tissue from patients^[22]. Evaluating inflammatory markers instead of CRP may help clarify the possibility relationship The relation between inflammation and the AF relapse following catheter ablation. Subsequent study found a strong association between elevated Interleukin-2 (IL-2) and interleukin-6 (IL-6) levels and recurrent AF. Two other

inflammatory indicators that have been connected to the frequency of recurrent Following catheter ablation, AF are tumour necrosis factor- α and matrix metalloproteinase-2 [22].

d. MicroRNAs: Heart fibrosis and atrial remodelling are two processes facilitated by microRNAs (miRNAs) in the progress of AF. miR-199a-5p and miR-22-5p circulating levels, that regulate the the heart's fibrogenic response, were shown to be greater in AF-positive HFrEF patients than in AF-negative patients^[23]. When left atrial enlargement is present, the likelihood of chronic AF has been associated with miR-21, which correlates with atrial fibrosis. A higher frequency of subclinical AF was connected to increased amounts of miR-1-3p, a myosin gene-regulatory associated with cardiac arrhythmogenesis, myocardial infarction, and hypertrophy^[23]. The expression levels of miRNA are genetically regulated and impact changes in tissue development. Variations in the control of miRNA expression levels in tissues and the bloodstream are linked to myocardial remodelling, exacerbating cardiovascular disease and triggering arrhythmogenic pathways. The development of AF in vivo has been demonstrated to be impacted by changes in miRNA expression, which result in improper calcium management, inflammation, and structural, electrical, and autonomic nerve remodelling. In miRNA genes, AF appears initiated and maintained by single nucleotide polymorphisms (SNPs)^[24].

4. EVIDENCE CONNECTING AF RISK WITH CARDIAC STRAIN BIOMARKERS:

hs-TnT with NT-proBNP could be the most efficient biomarkers for identifying individuals with symptomatic AF, who are situated at elevated hazard of fatality from all causes. All AF individuals who appear at the ED with increased hs-TnT or NT-proBNP levels should be thoroughly screened and given a more aggressive treatment regimen. ^[8].

Investigating Biomarker Levels in AF Patients:

The independent predictor of NT-proBNP is delayed clot lysis, a measurement of fibrinolytic plasma capacity, in non-anticoagulated individuals with AF, according to the current analysis, even after accounting for clinical and laboratory variables^[11]. Furthermore, the results of this study imply that Troponin T, and specifically NT-proBNP, may get used to identify AF individuals with a elevated burden of disease who possibly benefit from even more extensive therapy for their co-occurring disorders ^[12]. In contrast to the CHA2DS2-VASc and HAS-BLED scores, better predictive performance has been seen in several populations utilizing the ABC-bleeding and ABC-stroke scores (which incorporate NT-proBNP with hs-TnT). These ratings were created and authorized for use in the risk of AF patients assessment for bleeding and stroke, respectively ^[13].

There was no correlation between GDF-15, CA-125, and the length of AF detected, heart rate, dyspnoea, or renal function. These indicators were equally accurate as MR-proANP or NT-proBNP in diagnosing AF lasting shorter than 48 hours^[14].

5. CLINICAL IMPLICATIONS AND MANAGEMENT STRATEGIES:

Incorporating biomarkers into AF management protocols:

Anticoagulants, heart rate control drugs, electrical cardioversion, and antiarrhythmic drugs are all used in the outpatient treatment of AF in obese patients. Anticoagulants, antiarrhythmic drugs, and heart rate control medications are used in the outpatient treatment of AF in obese individuals. Left ventricular dysfunction can be brought on or made worse by both persistent AF and an uncontrolled ventricular rate. In any case, it could increase the death

risk for those with CHF, whose Both prevalence and incidence are continuously rising. A possible decrease in mortality must be demonstrated, even though some patients may experience better symptoms and improved left ventricular function following Atrioventricular junction radiofrequency ablation and implantation of a pacemaker. The Rhythm Follow-Up Study for AF Treatment trial aims to enrol 5,300 patients who will address the crucial question of rate vs rhythm treatment ^[33].

Lifestyle modification: A recent study has demonstrated that modifying one's lifestyle to prioritise physical activity, obesity management, and risk factor control can lessen the effects of AF. Eliminating Risk indicators (high blood pressure, obesity, hypoglycemia, sleep apnea, and smoking/alcohol behaviours) in obese patients with symptomatic AF reduced atrial remodeling load, symptoms, and episodes of AF^[30].

Rhythm control: Electrical cardioversion (ECV) and catheter radiofrequency ablation (CRFA) are two methods for rhythm control for AF that are considered in addition to pharmaceutical therapy. Age, symptoms, and the existence of cardiac disease all have an impact on the specific indications and efficacy of each technique. Higher body weight patients had decreased success with ECV, perhaps because less energy reaches the atria; nevertheless, success rates can be increased by increasing energy levels. Nevertheless, no differences were found in the findings of AF cryo-balloon ablation between patients who were obese and those who were not. Obesity has a mixed influence on CRFA results; whereas some studies link obesity to increased recurrence, procedural failure, and complications, others demonstrate effectiveness as well as enhancements in quality of life. A 40 kg/m² BMI or above more is the only one that consistently lowers CRFA success. Although initial outcomes are inconsistent, there is a lack of information on more recent methods such as cryo-balloon and pulsed-field ablation. Thus, early rhythm control may help obese AF patients; however, the optimal approach is yet unknown, requiring more research^[36].

Anti-coagulation drug: Obesity affects the risk of AF and can change how patients are managed. Anticoagulation is a fundamental component of AF therapy, aimed at reducing the risk of thromboembolic consequences linked to the illness. A recent study that reviewed the dosage of warfarin in patients categorized by body mass index found that individuals with high BMI—especially those who weighed more than 40 kg/m²—needed far more warfarin. If warfarin is started while the patient is in the hospital, a greater weekly dose may affect how long the patient stays in the therapeutic range. DOACs, or direct oral anticoagulants,

include dabigatran., apixaban, rivaroxaban, and edoxaban, appear to be the solution to this issue when used for the prophylaxis of thromboembolism ^[29].

Antiarrhythmic Drugs: Class I AADs, commonly used to treat symptomatic AF, block the cardiac sodium channel, which has clinical consequences for AF management in obese patients. There is growing evidence that obesity suppresses the sodium current and as a result, giving class I AADs to obese patients who have AF symptoms may further reduce sodium current and may cause pro-arrhythmias, which would paradoxically aggravate the incidence and/or maintenance of AF^[35].

Sodium-glucose co-transporter 2 inhibitors (SGLT2i): Sodium-glucose co-transporter 2 inhibitors are a further class Some diabetes medications that are being studied; these drugs can be used to treat or prevent AF in individuals who are overweight. Dapagliflozin, for instance, has a proven impact on EAT volume reduction in addition to weight loss. By reducing serum TNF- α levels in diabetics, it also showed to have anti-inflammatory properties. Further research is necessary to determine the effectiveness of these medications in lowering obese people's chance of developing AF ^[35].

Anti-inflammatory Drugs: By serving as anti-inflammatory mediators, monoclonal antibodies that target human IL-1 receptor antagonists, like anakinra and rilonacept, as well as IL-1 β (canakinumab and gevokizumab), may be able to lower the incidence of AF ^[30]. It was determined whether Canakinumab could lower cardiovascular events among people with increased CRP and previous episodes of myocardial infarction through the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial. Canakinumab lowered cardiovascular events and plasma CRP levels^[31]. Additionally, there was a correlation found between cardiovascular events and plasma CRP levels. Canakinumab may potentially work to stop AF from happening^[32].

6. CONCLUSION:

In conclusion, cardiac strain biomarkers offer a promising tool for improving the risk stratification of AF-obese patients. Their ability to detect early myocardial dysfunction provides a significant advantage over traditional methods, potentially leading to better prevention and management of AF. Addressing the current challenges and conducting further research will be essential to fully harness these biomarkers' potential in clinical practice.

By advancing our understanding and application of cardiac strain biomarkers, we can move towards more personalised and effective strategies for preventing and managing AF in the growing population of obese patients.

DISCUSSION:

The discussion section of this review article examines the role of cardiac strain biomarkers in the risk stratification of AF in obese patients. It synthesizes findings, addresses limitations, and explores future directions for research and clinical practice.

Left atrial strain and global longitudinal strain (GLS) are two examples of cardiac strain biomarkers that provide an advanced way to evaluate myocardial function. These indicators can identify minor changes in cardiac function before the emergence of clinical symptoms in obese patients, who are at heightened risk for AF due to volume overload and elevated left atrial pressure. Early identification is essential for prompt intervention and potentially lowering the frequency of AF.

When patients are obese, traditional echocardiographic measurements such as ejection fraction (EF) frequently miss the early signs of myocardial dysfunction. With higher sensitivity and specificity, cardiac strain biomarkers offer a more complex understanding of myocardial mechanics. Research has demonstrated the importance of impaired left atrial and decreased global longitudinal strain (GLS) in predicting incident AF in obese persons, highlighting their predictive power in clinical practice.

One way to improve AF risk stratification in obese patients is to include heart strain assessment in routine clinical examinations. During echocardiographic evaluations, this integration would entail the routine use of cutting-edge imaging methods like speckle-tracking echocardiography. Clinicians might then create a more thorough risk profile by combining these biomarkers with conventional risk variables like age, diabetes, and Hypertension.

Utilizing strain biomarkers to identify obese people at high risk for AF may result in early and more focused therapies. These could include dietary adjustments intended to lower cardiovascular risk, weight loss, and increased physical activity. Results from strain biomarkers may also inform more severe therapies such as catheter ablation, as well as pharmacological approaches to control obesity-related comorbidities.

Heart strain biomarkers have a lot of potential, but a few problems need to be worked out before they can be widely applied in clinical practice. Major challenges include the lack of recognized normal values for obese individuals, the unpredictability of imaging technologies, and the need for specific training to interpret strain measurements appropriately. Moreover, the expense and availability of contemporary imaging methods may limit their widespread application.

To confirm the predictive significance of heart strain biomarkers in a variety of obese populations, future research should concentrate on large-scale, longitudinal investigations. Standard operating procedures must be established to measure and interpret strain. A more thorough risk assessment tool may also be obtained by examining the interactions between cardiac strain biomarkers and other new biomarkers, such as circulating cardiac biomarkers (like troponins and NT-proBNP).

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