**Case Presentation**

A 68-year-old man presents to his primary care physician describing an irregular and rapid heartbeat that has awakened him from sleep. The patient has a blood pressure of 148/92 mm Hg, a body mass index (BMI) of 35.5 kg/m², and a history of diabetes mellitus that has been managed with oral glycemics. On auscultation, the physician appreciates occasional irregular beats without a cardiac murmur. An ECG shows normal sinus rhythm with a PR interval of 180 milliseconds and infrequent premature atrial contractions. A 24-hour Holter monitor identifies intermittent premature atrial contractions and demonstrates paroxysmal atrial fibrillation (AF) that is primarily nocturnal. The patient’s inquires about (1) how obesity has contributed toward his developing AF, and (2) whether weight loss would ameliorate the risk of AF or the burden of the arrhythmia.

**Background: Obesity Is a Well-Described Risk Factor for AF**

Obesity is a profound public health concern with increasing prevalence. AF is the most commonly encountered clinical arrhythmia and results in multiple adverse sequelae that include stroke, heart failure, cognitive decline, dementia, diminished quality of life, and death.¹ In community- and population-based cohort studies, obesity has consistently emerged as a risk factor for AF. In comparison with normal-weight referents, obese individuals have up to a 2.4-fold increased AF risk.² In cardiothoracic surgery cohorts, the postoperative risk of AF ranges from a 1.4- to 2.4-fold increased risk in comparison with nonobese referents.³,⁴ The risk of AF increases progressively with rising BMI. In a large cardiothoracic surgery series, individuals at the extreme of BMI (≥40.0 kg/m²) had a 2.3-fold increased postoperative AF risk in comparison with a 1.2-fold increased risk in the overweight (BMI 25–30 kg/m²).⁴ An observational cohort from the Mayo Clinic similarly showed increased likelihood of transitioning from paroxysmal to permanent AF with progressive increase in BMI.⁵ BMI has emerged as relevant to longitudinal AF risk in multiple AF risk scores developed in community-based cohorts.⁶⁻⁸ Two of the risk scores were conducted in biracial cohorts, thereby enhancing their generalizability.⁷,⁸ Figure 1 presents the Framingham Heart Study 10-year AF risk calculator for the patient described in the case presentation (http://www.framinghamheartstudy.org/risk/atrial.html). The patient’s 10-year AF risk is calculated as 18%. In addition to systemic adiposity, regional adipose tissue deposition, specifically epicardial adipose tissue volume measured by computed tomography or MRI, has emerged as a potent risk factor for AF. The effect of epicardial fat is independent of BMI and other known risk factors for AF.⁹ The epidemiological data summarized here consistently indicate that obesity is associated with a substantial risk for the development of AF. A meta-analysis reported that obese individuals have a 49% increased risk of AF in comparison with nonobese individuals.¹⁰ Of paramount importance is that obesity is one of the very few modifiable risk factors for AF that have been identified.

Future research is essential to understand better the epidemiological associations of obesity and AF. The Table
provides a summary of future directions in obesity and AF research.

**Obesity and AF: Shared Risk Factors, Shared Intermediates**

Obesity and metabolic disease have multifactorial contributions toward AF risk. Figure 2 describes the overlapping relation between obesity, AF, and their common, foremost clinical correlates. Hypertension, strongly associated with obesity, is a well-described risk factor for AF; the incidence of hypertension increases alongside body weight and progressive rise in obesity class. Cardiovascular disease, comprising both macro- and microvascular ischemia, is a second, highly prevalent intermediate linking obesity and AF. Central obesity constitutes part of the metabolic syndrome, and, in a community-based cohort, additional metabolic syndrome components increased the 10-year risk of incident AF to 4-fold when all 5 were present.\(^{11}\) Obstructive sleep apnea (OSA) merits increased emphasis for its association with nocturnal arrhythmias and for its being a highly prevalent comorbidity of obesity. In obese cohorts, the prevalence of OSA extends up to 90\%.\(^{12}\) OSA promotes sympathetic overactivity, vascular inflammation, and heart rate variability and has associations with hypertension and metabolic risk factors. Figure 3 includes intermediate steps to suggest the multiple clinical pathways through which obesity may result in AF pathogenesis.

**Back to Our Case**

The patient instituted the Dietary Approaches to Stop Hypertension
(DASH) diet and received medical clearance for exercise. Over the next 2 years, he was able to reduce his BMI to 32.5 kg/m². He used antiobesity agents (e.g., tetrahydrolipstatin, or Orlistat) that work to reduce fat absorption in the gut. His history of AF precluded use of phentermine, an appetite suppressant. He developed pronounced dyspnea on exertion, and repeated ECGs and another Holter monitor now showed persistent AF. The patient’s CHA₂DS₂-VASc score was calculated as 3 (1 point each for history of hypertension, diabetes mellitus, and age 65–74), and he was started on long-term oral anticoagulation in addition to continuing a daily aspirin. He underwent an elective cardioversion and was started on sotalol with appropriate monitoring for QT-interval prolongation and bradyarrhythmia.

Obesity and Cardiovascular Remodeling

Cardiovascular remodeling secondary to obesity is a critical focus of investigation, identifying intermediate steps in the pathway between exposure and outcome. Atrial remodeling may be summarized as a heterogeneous process characterized by disruption of atrial electric integrity secondary to long-term clinical exposures. Alterations in atrial electrophysiological function and concomitant remodeling are maladaptive responses to the resulting metabolic, hemodynamic, and ischemic stresses. The cumulative results are electric disturbances, structural modification, and inflammation that promote interstitial atrial fibrosis and yield a proarrhythmic substrate. Obesity is associated with a 2.4-fold 10-year risk of echocardiographic left atrial volumetric enlargement. Ventricular diastolic function further impacts atrial integrity. Obesity and hypertension may yield ventricular hypertrophy, which in turn alters diastolic function, raising atrial pressures and promoting atrial remodeling. The up-stream mediators of atrial remodeling from obesity are shown in Figure 3.

P-wave indices are derived from the surface ECG and are vectorcardiographic measurements of P-wave
morphology, duration, and amplitude. They provide a low-cost, reproducible measurement of atrial electric function. P-wave indices are progressively altered by obesity and waist circumference. Figure 4 shows the cubic restricted splines that graphically display the relation between BMI and maximum P-wave duration as continuous variables in a large, biracial cohort (n=14433).14 A single-center, small (n=63) study reported significant differences in atrial and pulmonary vein electrophysiology between obese and nonobese individuals.15 Obese individuals had shorter atrial and pulmonary vein refractory periods than nonobese individuals, suggesting a proarrhythmic substrate.

**Biomarkers and Intermediate Pathways Relating Obesity and AF**

Inflammatory biomarkers, increased in obesity, are an alternative avenue for relating obesity and AF pathogenesis. C-reactive protein has likely been best studied and characterized for its relation to AF. Pericardial fat, overlying atrial tissue, has received attention for its relation to obesity, adipocytokine expression, and correlation with inflammatory markers.

**Genomics of Obesity and AF**

We are at the frontier of integrating genomics in the examination of the relation of obesity and AF.

**Case Conclusion**

The patient, now 70 years of age, regained his previous weight. He reported continued dyspnea and daytime drowsiness. He underwent polysomnography that diagnosed OSA and during which he was in continuous AF. Anticoagulation for stroke prevention was continued. He was taken off sotalol, given his persistent AF while on the medication, and referred for electrophysiological ablation to treat symptomatic AF.

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**References**


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