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EDITORIAL COMMENT

Atrial Fibrillation and Body Composition

Is it Fat or Lean That Ultimately Determines the Risk?*

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Atrial fibrillation (AF) is the most common sustained arrhythmia and is responsible for considerable morbidity and mortality (1). Improved information from epidemiological, clinical, preclinical, and translational studies is needed to aid in developing better approaches to AF prevention and treatment (1,2).

OBESITY AND AF

The Manitoba Follow-Up Study first identified obesity as a risk factor for AF over 20 years ago (3). Since then, numerous studies have shown that obesity increases the likelihood of AF development (4). Weight loss, whether as part of a structured risk-factor intervention program (5) or as a result of bariatric surgery (6), reduces AF risk. Preclinical studies have suggested a variety of potential mediating mechanisms for the AF-promoting effects of obesity. In a genetic rat model of leptin-deficient obesity, ventricular diastolic dysfunction predisposes to left-atrial dilation that mediates AF promotion (7). Sheep with obesity due to overfeeding develop atrial electrophysiological, electroanatomic, and structural remodeling, along with increased occurrence and sustainability of AF (8). Furthermore, there is evidence that adipocytes produce biologically active molecules that directly promote the development of atrial fibrosis (9), a common link between cardiovascular risk factors and AF promotion (1). Additional factors are specifically implicated in AF-promoting effects of epicardial fat, including proinflammatory signaling, oxidative stress, autonomic changes, and direct modulation of the electrophysiological properties of cardiomyocytes through contact with infiltrating adipose tissue (10).

BODY HABITUS AND AF

Although obesity is the anthropometric feature most associated with AF, other aspects of body habitus have also been associated with the arrhythmia. Hanna et al. (11) hypothesized that stature might be associated with AF on the basis of the well-recognized importance of left atrial size as an atrial arrhythmia determinant. In a multivariable analysis of factors associated with AF occurrence in a registry of >25,000 patients with left ventricular dysfunction, height was independently associated with AF risk. Body surface area was also an independent predictor. The independent association between height and AF risk was confirmed in a broader population with data from the Cardiovascular Health Study (12). Interestingly, the known sex predilection of men to AF was completely eliminated by controlling for height.

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LEAN BODY MASS AS A POSSIBLE COMMON DENOMINATOR

One of the difficulties in analyzing the role of different aspects of body habitus is their obvious inter-relationship. Greater height is associated with greater weight, greater body surface area, and so on. In this issue of the *Journal*, Fenger-Grøn et al. (13) present the results of an interesting approach to the analysis of anthropometric contributors to AF.

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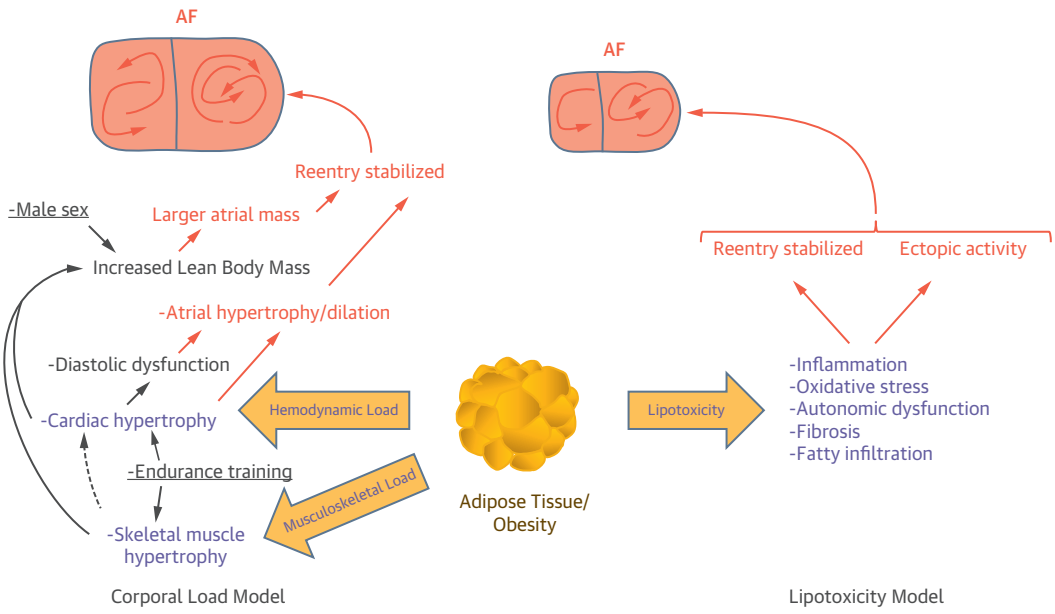
FIGURE 1 Possible Mechanistic Relationships Between Obesity and AF



Much recent research suggests that obesity leads to atrial fibrillation (AF) based on a variety of cardiac remodeling effects produced by products of adipose tissue, the "Lipotoxicity" model. On the other hand, the Fenger-Grøn et al. (13) results suggest a key role for the effects of obesity on lean body mass (the "Corporal Load" model), which acts to increase atrial size and mass, and thereby stabilize AF. The Corporal Load model may also explain, at least in part, how male sex and exercise training promote AF, because both increase lean body mass.

They take advantage of a large Danish registry of patients enrolled between December 1993 and May 1997 and followed longitudinally for a median of 16.3 years. All patients were subjected to bioelectrical impedance analysis at baseline to obtain fat and lean body mass estimates. Patients with malignancies or an AF history at baseline, or those not providing full lifestyle information, were excluded, leaving a study group of 55,273. The primary outcome was new-onset AF or flutter. Nine anthropometric measures were analyzed for association with AF or flutter: lean body mass; fat mass; percentage of fat; height; weight; body mass index; hip circumference; waist circumference; and waist-to-hip ratio. Each anthropometric variable showed significant univariate association with AF risk; adjustment for each of the other characteristics failed to affect the association between lean body mass and AF risk, but adjustment for the effect of lean body mass eliminated the association with AF for each of the other characteristics. Full adjustment for all other anthropometric variables and a wide range of potential modulators (sex, smoking status, educational level, physical activity, fruit and vegetable intake, alcohol consumption, total energy intake, and comorbidities) resulted in a weak U-shaped relationship that failed to reach statistical significance for fat mass. In contrast, there was a strong, graded relationship between lean body mass and AF over a relative-risk range from about 0.45 to about 1.75. These results suggest that lean body mass is, by far, the strongest anthropometric determinant of AF risk, and that the relationships with other anthropometric factors are mediated through their effect on lean body mass.

MECHANISTIC AND POTENTIAL CLINICAL SIGNIFICANCE. The Fenger-Grøn et al. (13) study is well done and has interesting implications. First, the results indicate that lean body mass is by far the strongest anthropometric determinant of AF risk. The mechanism(s) linking larger lean body mass to AF are not established. However, over 100 years ago, Garrey (14) suggested that a critical mass of tissue is needed to maintain fibrillation. Subsequent work in a range of animals supported the notion that atrial size is a key determinant of AF persistence (15). Simulation studies suggest that larger atria may make AF more stable by allowing for a larger number of rotors, so that even if rotor stability is limited, the continuous creation of daughter rotors is sufficient to prevent AF extinction (16). Thus, the simplest explanation of

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