JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 66, NO. 1, 2015
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2015.04.057

EDITORIAL COMMENT

Atrial Fibrillation and Obesity

Not Just a Coincidence*

Stéphane N. Hatem, MD, PhD

The risk of developing atrial fibrillation (AF) is increased in obese patients. This has been well established by several epidemiological studies. For instance, the long-term follow-up of the Framingham Heart Study reported that every unit increase in body mass index (BMI) raises AF risk by 4% (1–5). At first glance, this epidemiological observation could be explained by the fact that obesity is often associated with enlarged left atria, ventricular dysfunction, and hypertension, all of which can generate a susceptible AF substrate (6). Sleep apnea and autonomic dysfunction—often present in obese patients—could also contribute to increased AF risk. However, the relationship between obesity and AF may not only be due to the coincidental accumulation of common comorbidity factors between the 2 clinical entities, but rather to the specific effects of obesity on the structural and functional properties of the atrial myocardium (7). Obesity is a systemic disease characterized by low-grade inflammation, increased renin-angiotensin-aldosterone system and endothelin pathway activities, as well as higher levels of transforming growth factor (TGF)-β1. These factors are coupled to signaling pathways involved in hypertrophy and fibrosis of the myocardium, and therefore support the possibility that obesity could be another distinct risk factor for AF.

In this issue of the *Journal*, the article by Mahajan et al. (8) explores the nature of the link between weight gain and AF. Obese sheep maintained on a high-calorie diet for 72 weeks showed a typical AF substrate, with left atrial dilation, conduction abnormalities, fractioned electrocardiograms, and an abnormal vulnerability to AF. Diffuse interstitial

SEE PAGE 1

fibrosis of the atrial myocardium is observed at the tissue level, probably explained by the 5-fold increase in local TGF-β1 expression. But the most exiting finding arising from this study is that obesity is associated with a distinct AF substrate, as a result of fatty infiltration of the abundant adipose tissue contiguous to epicardial adipose tissue into the atrial myocardium. This fatty infiltration predominates in the posterior wall of the left atria, at the junction of the pulmonary veins. Using endocardial mapping, the authors found that the posterior wall of the fatty infiltrated myocardium generated low and heterogeneous voltage. It is possible that the infiltration of adipose tissue alters the functional organization of the atrial myocardium, resulting in local conduction block and depressed excitability, as has been described for the ventricular myocardium (9). In addition, adipose tissue produces a myriad of inflammatory cytokines, chemokines, adipokines, and growth factors, which can freely diffuse into the adjacent myocardium and modify its structural and functional properties (10–12). For instance, epicardial adipose tissue secretes activin A, a member of the TGF family, which has a fibrotic effect on the atrial myocardium (12).

What is the origin of this fatty infiltration? It could be caused by a nonspecific general process of ectopic fat accumulation, as overwhelmed subcutaneous adipose tissue attempts to clear excess triglycerides in obese patients (13). It could also result from the activation of local and specific mechanisms in response to various myocardial hemodynamic or metabolic stresses. In support of this assumption,

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Department of Cardiology, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital INSERM-UPMC UMRS_1166 and Institute of Cardiometabolism and Nutrition, Paris, France. Dr. Hatem is funded by the European Network for Translational Research in AF (FP7 collaborative project EUTRAF, No 261057); the Fondation Leducq "Structural Alterations in the Myocardium and the Substrate for Cardiac Fibrillation"; the French National Agency through the National program "Investissements d'avenir" with reference ANR-10-IAHU-05 (SNH), and the "Fondation de France."

atrial fat accumulation is now recognized as a predictor of the risk and severity of AF, independent of obesity, suggesting crosstalk between the atrial myocardium and adipose tissue (14). For instance, both rapid atrial pacing and AF induce the expression of several adipocyte-related genes that can regulate adipose tissue accumulation (15).

The study by Mahajan et al. (8) has 2 potential clinical implications. First, advances in cardiac imagery should lead to an improved ability to visualize myocardial fat depositions, and consequently aid in the detection of AF substrates in both obese patients and those with metabolic syndromes. Second, weight loss could have a beneficial effect on atrial remodeling and AF substrate formation. Interestingly, 5 months after bariatric surgery, epicardial fat volume diminishes, the left atrium reduces in size, and ventricular diastolic filling properties are improved (16). Taken together, the observation that obesity and adipose tissue dysregulation can have a direct impact on the structure and physiological properties of the atrial myocardium justifies study into the effects of upstream and personalized therapies on AF substrate progression and arrhythmia occurrence in overweight patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Stéphane N. Hatem, INSERM-UPMC UMR_S1166, Faculté de Médicine, 91, Boulevard de l'hôpital, 75013 Paris, France. E-mail: stephane.hatem@upmc.fr.

REFERENCES

1. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292:2471–7.

2. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005;118:489–95.

3. Dublin S, French B, Glazer NL, et al. Risk of new-onset atrial fibrillation in relation to body mass index. Arch Intern Med 2006;166:2322–8.

4. Tedrow UB, Conen D, Ridker PM, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation: the WHS (Women's Health Study). J Am Coll Cardiol 2010;55:2319–27.

5. Tsang TS, Barnes ME, Miyasaka Y, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J 2008;29:2227–33.

6. Ito K, Date T, Kawai M, et al. Morphological change of left atrium in obese individuals. Int J Cardiol 2011;152:117–9.

7. Abed HS, Samuel CS, Lau DH, et al. Obesity results in progressive atrial structural and electrical remodeling: Implications for atrial fibrillation. Heart Rhythm 2013;10:90–100.

8. Mahajan R, Lau DH, Brooks AG, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. J Am Coll Cardiol 2015;66:1–11.

9. Pouliopoulos J, Chik WW, Kanthan A, et al. Intramyocardial adiposity after myocardial infarction: new implications of a substrate for ventricular tachycardia. Circulation 2013;128:2296–308.

10. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005;2:536–43.

11. Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003;108:2460–6.

12. Venteclef N, Guglielmi V, Balse E, et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipofibrokines. Eur Heart J 2015;36:795–805.

13. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–7.

14. Al Chekakie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. J Am Coll Cardiol 2010;56:784–8.

15. Chilukoti RK, Giese A, Malenke W, et al. Atrial fibrillation and rapid acute pacing regulate adipocyte/adipositas-related gene expression in the atria. Int J Cardiol 2015;187:604–13.

16. Gaborit B, Jacquier A, Kober F, et al. Effects of bariatric surgery on cardiac ectopic fat: lesser decrease in epicardial fat compared to visceral fat loss and no change in myocardial triglyceride content. J Am Coll Cardiol 2012;60:1381–9.

KEY WORDS activin A, adipose tissue, atrial myocardium, atrial remodeling