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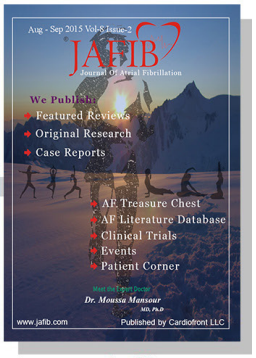

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Review Of Obesity And Atrial Fibrillation: Exploring The Paradox

González-Cambeiro, María Cristina, Rodríguez-Mañero, Moisés, Abu-Assi, Emad; Raposeiras-Roubin, Sergio, González-Juanatey, José Ramón.

Servicio de Cardiología y Unidad Coronaria, Hospital Clínico Universitario de Santiago de Compostela, Spain.

Abstract

There is a well established association between obesity and atrial fibrillation (AF). Nevertheless, the effects of obesity in the outcomes of patients with AF has not been investigated since a few years before. In this regard, several studies have demonstrated a better clinical prognosis of AF in overweight and obese populations.

In the present manuscrit, we aimed to explore the main articles in which the "obesity paradox in AF" was found.

Obesity Burden

The prevalence of obesity has increased dramatically worldwide over the last decades and has now reached epidemic proportions. For instance, the global prevalence of obesity has nearly doubled between 1980 and 2008. According to the World Health Organization (WHO), 35% of adults worldwide aged more tan 20 years were overweight (34% men and 35% women) in 2008, including 10% men and 14% women being considered as obese. Prevalence is particularly high in America with a high proportion of overweight and obesity (62% and 26% respectively in both sexes and 3% for obesity).[1]

In the United States, the prevalence of obesity has increased by 8% between 1976 and 1980, by another 8% between 1988 and 1994 with similar increases between 1988-1994 and 1999-2000. In contrast, data from the last decade.[1999-2010] suggest that the prevalence of obesity may have plateaued in the USA.[2-4]

According to the latest National Health and Nutrition Examination Survey (NHANES), the age-adjusted obesity prevalence was 35.7% in the USA in 2010 with no sex differences. Extreme obesity has more than doubled since 1988-19944-5.

Such growing numbers are a source of concern since the negative consequences of obesity start as early as in childhood. Indeed, some experts predict a decrease life expectancy at birth in the USA during the first half of the 21st century[6].

Each year, 28 million individuals are dying from the consequences of overweight or obesity worldwide1. High body mass index (BMI) is associated with the development of cardiovascular (CV) risk factors such as hypertension, dyslipidemia, insulin resistance, and diabetes mellitus, leading to cardiovascular diseases (CVD) such as coronary heart disease and ischemic stroke.[7-9] The development of the comorborbidities is proporcionate to the BMI and obesity is considered as an independent risk factor for CVD.[10-11]

Several studies have documented that a high BMI is significantly associated, both in men and women, with manifestations of CVD such as angina, myocardial infarction, heart failure and sudden death.[12-13]

The higher incidence of CV events in obese patients seems to be related to endotelial dysfunction and subclinical inflammation in addition to the worsening of CV risk factors.[14] Overall, obesity is associated with an increased mortality rate15, but obesity grades must be considered in risk stratification. In a recent meta-analysis including 2.88 millions of individuals, all obesity grades combined were associated with an increased mortality rate, with an hazard ratio (HR) of 1.18 (95% confidence interval [CI], 1.12-1.25). However, when analyzed separately, obesity grade 1 was not associated with an increased mortality risk, with a HR of 0.97 (95% CI 0.90-1.09), compared to normal weight. In contrast, severe obesity (grades 2 and 3) was associated with and increased mortality risk (HR of 1.34-95% CI, 1.21-1.47).[16]

Atrial Fibrillation Epidemiology

Atrial fibrillation is the most common sustained cardiac arrthythmia, occurring in 1-2% of general population. Over 6 million European individuals suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages.[17]

AF confers a 5-fold risk of stroke, and one in five of all strokes is attributed to this arrhythmia. Ischaemic strokes in association

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Corresponding Author:
González-Cambeiro, María Cristina, MD
Servicio de Cardiología y Unidad Coronaria
Hospital Clínico Universitario de Santiago de Compostela, Spain
Street Choupana (without number)
15706, Santiago de Compostela

with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. The risk of death from AF-related stroke is doubled and the cost of care is increased 1.5-fold. The prevalence of AF increases with age, from less tan 0.5% at 40-50 years, to 5-10% at 80 years. Men are more often affected tan women. It is well known that AF is associated with increased rates of death, stroke and other thrombo-embolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity and left ventricular dysfunction.[17]

AF is associated with a variety of medical conditions, which promote an additive effect on its perpetuation. Some of them described are ageing, hypertension, symptomatic heart failure, valvular heart diseases, coronary artery disease, thyroid dysfunction, diabetes mellitus, sleep apnea, chronic renal disease and obesity. Obesity is found in 25% of AF patients 15 in a large german AF registry.[17]

Above-mencioned data indicate that both, obesity and AF, are contemporary interlinked epidemics and will suppose a large public health burden in the future.

Prior studies have examined the relationship between obesity and AF.[18-21] Obese people have a 1.5 times higher risk of developing AF as compared with normal weighted individuals when BMI is considered as a categorical variable. Also, when BMI is investigated as a continuous variable, each unit increase in BMI has been associated with 4% increase in new-onset AF.[18-21] Although the precise mechanism for this association is not well understood, changes in atrial and ventricular structure diastolic function, autonomic function, and increased total blood volume might play a role.[22-26]

Furthermore, obesity is associated with left atrial enlargement, which is considered an "intermediate phenotype" for AF.[21] Obesity also is implicated as a risk factor for progression of paroxismal to permanent AF.[27] Although catheter ablation is successful in obese patients28, they often require more than twice the effective radiation dose as compared with normalweighted patients29. Also, obstructive sleep apnea (OSA), and its association with obesity, has been correlated with increased incidence, prevalence and recurrence of AF.[30-33]

Despite overwhelming data linking obesity and AF, the effect of obesity on outcomes in AF patients has not been investigated since a few years ago.

Obesity was traditionally associated with a higher prevalence of several medical diseases, worst outcomes and increased mortality rate. Surprisinly, recent studies in obese populations have shown positive results in terms of CV hospitalization, global and CV mortality. This has been termed as the "obesity paradox" in an attempt to reflect the paradoxical association between overweight, obesity and a more favorable prognosis, is poor understood but has been observed consistently in patients with established CV disease, including chronic coronary heart disease34, acute myocardial infarction,[35-36] acute and chronic heart failure35-39, peripherial arterial disease40, hypertension, chronic obstructive pulmonary disease41, and more recently in AF.[42-45]

Available Data

In a sub-analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study44, an inverse relationship between obesity and prognosis was described. A total of 2.492 patients were analyzed. BMI was evaluated as a categorical variable (normal 18.5 to <25 kg/m2, overweight 25 to <30 kg/m2 and obese ≥30 kg/m2) under the World Health Organization definition. Accordingly, the rate of all-cause death was higher in the normal BMI group (5.8 per 100 patient-years) than in the overweight and obese groups (3.9 and 3.7, respectively). In this study, CV death rate was also highest in the normal BMI group (3.1 per 100 patient-years), lowest in the overweight group (1.5 per 100 patient-years), and intermediate in the obese group (2.1 per 100 patient-years), being overweight associated with lower risk of CV death (HR 0.47, p=0.002). After adjustment for baseline factors, differences in risk of death from any cause were no longer significant.

At the same time, Apurva O. Badheka et al[43] performed a post hoc analysis of the AFFIRM study, where the same population of 2492 patients was analyzed. Patients with BMI ≥18.5 were slip into normal (18.5-25 kg/m2), overweight (25-30 kg/m2), and obese (≥30 kg/m2) categories as per BMI. Multivariate Cox proportional hazards regression was used in this cohort. Endpoints were all-cause mortality and CV mortality. They report 304 deaths (103 among normal weight, 108 among overweight, and 93 among obese) and 148 CV deaths (54 among normal weight, 41 among overweight and 53 among obese) over a mean period of 3 years of patient follow-up. On multivariate analysis, overweight (HR 0.64; 95% CI, 0.48-0.84; p=0.001) and obese (HR 0.80; 95% CI, 0.68-0.93; p=0.005) categories were associated with lower all-cause mortality as compared with normal weight. Overweight (HR 0.40; 95% CI, 0.26-0.60; p<0.01) also had lower CV mortality as compared with normal weight patients.

In a recent study performed by the AFBAR (Atrial Fibrillation Barbanza Area) research group,[42] obesity, defined as a BMI ≥30 kg/m2, was associated with better prognosis in a community-based cohort of patients with AF. A total of 746 patients who were prospectively included were studied. They were categorized into 3 BMI groups using baseline measurements: normal weight (<25 kg/m2), overweight (25-30 kg/m2), and obese (≥30 kg/m2). Survival free from the composite endpoint hospitalization for CV causes or all-cause mortality was compared across the 3 BMI subgroups. A multivariate Cox proportional hazard regression was also performed to determine the independent effect of obesity as well as overweight, with respect to normal BMI as a reference category regarding the study endpoint. Median follow-up time was 36 months. In this population, 49.3% were obese and 38.2% had overweight. The composite endpoint rate was 70.9%, 67.5% and 57.6% for obese, overweight and normal weight patients respectively (log rank test; p=0.02). An inverse association of obesity with a favorable prognosis persisted even after multivariate adjustment: HR 0.668; 95% CI, 0.449-0.995; p=0.0047. HR of overweight, however, was 0.741; 95% CI, 0.500-1.098; p=0.096.

Finally, in a recent study, Juan Wang et al[45] also found an obesity paradox in patients with AF and heart failure. They enrolled 806 patients with AF who were divided into 4 different BMI categories according to Chinese Obesity Working Group: underweight (<18.5 kg/m2, n=101 [12.5%]), normal weight (18.5 to 24 kg/m2, n=230 [28.5%]), obese (≥28 kg/m2, n=102 [12.7%]). The endpoints for current analyses were all-cause death and CV mortality during the 12-month follow-up. Univariate and multivariate Cox regression analyses were performed. A total of 153 deaths and 113 CV deaths occurred. All-cause mortality risk is lower in patients with overweight (HR 0.41, 95% CI, 0.26-0.64, p<0.001) and obesity (HR 0.46, 95%

CI, 0.25-0.83, p=0.011) compared to patients with normal weight. CV mortality risk is lower in overweight (HR 0.43, 95% CI, 0.26-0.73, p=0.002) and obese (HR 0.49, 95% CI, 0.24-0.97, p=0.042) patients. After adjustment for multiple relevant co-variables, as a continuous variable, BMI was not a risk factor for all-cause mortality (HR 0.91, 95% CI, 0.87-0.95, p<0.001), and for CV mortality (HR 0.91, 95% CI, 0.86-0.96, p<0.001). As a categorical variable, obesity (HR 0.50, 95% CI, 0.26-0.94, p=0.032) and overweight (HR 0.40, 95% CI, 0.25-0.63, p<0.001) were significantly associated with a lower risk of all-cause mortality, and overweight also with a lower CV death (HR 0.45, 95% CI, 0.26-0.76, p=0.003) compared to normal weight patients.

Obesity Paradox Controversies

On the basis of previously named studies, a better prognosis in overweight and obese patients with AF has been demonstrated. Nervertheless, the potential mechanism of this obesity paradox has not been fully elucidated. Several hipotheses had been proposed in this regard.

Inflammation and increased inflammatory markers are believed to cause AF initiation and maintenance.[46] It seems that the cell signaling protein called Tumor Necrosis factor alpha (TNFα), can increase the pulmonary vein arrhythmogenicity thereby causing inflammation-related AF. Because adipose tissue produces TNFαtype I and II receptors, this could result a anti-arrythmogenic milieu in obese patients with AF.[47,48]

The called "Endotoxin-Lipoprotein hypothesis", states that obese patients have higher cholesterol and lipoprotein levels, which could remove proinflammatory toxins causing a subsequent inflammatory state reduction, although the applicability of this hypothesis in AF is not clear.[49] Atrial natriuretic peptide levels are importantly increased in AF and predict mortality in advanced heart failure patients with AF.[50,51] Low circulating natriuretic peptide levels found in obese patients could be also related with better outcomes.[52]

The activation of renin-angiotensin system has been associated with atrial fibrosis and electrical remodeling in AF.[53] Obese people with AF may have diminished levels as compared with lean patients, which may improve long-term CV outcomes.[54]

The higher blood pressure levels seen in overweight and obese patients may allow for a greater and fast uptitration of therapies such as αblockers and angiotensin-converting enzyme inhibitors, drugs with demonstrated life-extending properties in AF patients.[55]

On the other hand, it is well known that higher body fat and especially higher lean mass index (LMI) may be associated with muscular strength, linked to favorable prognosis and better survival. Many epidemiological studies were unable to show a higher risk for adverse events in overweighed patients. This could be explained by the limited ability of BMI to differenciate body fat from lean mass.[56-58]

Studies Limitations

Based on its design, we cannot relate the results of the epidemiological studies with the proposed theories previously discussed. It will deserve further investigation in order to explain the mechanism why this particular subgroups of patients, despite the higher rates of diabetes and hypertension, presented better outcomes. These positive results can create doubts about whether current recommendations for CV prevention should be extrapolated to populations with established CVD.

Finally, it should be highlighted that the results of these studies should be considered in light of its potential limitations. First, conclusions are based in the BMI, a parameter that it is known does not differenciate body fat from lean mass. Second, they were ultimately unable to account for fat distribution (peripheral versus abdominal obesity) and other measures of adiposity such as body fat percentage. Besides, information regarding the proinflammatory and nutritional status were not collected, and potential changes in BMI over the study follow-up were not considered.

Conclusions

Overweight, defined as a BMI 25-30 kg/m2, and obesity, defined as a BMI ≥30 kg/m2, according to the WHO, were found to be associated with a better prognosis in terms of CV hospitalizations, global and CV mortality risk in previous studies which included an important number of AF patients. These results should be analyzed under de BMI parameter limitations. Thus, further prospective and randomized studies specifically designed to address this point will be needed to explain the etiopathogenic mechanisms underlying the called "obesity paradox in AF".

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