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Atrial fibrillation and obesity: two epidemic diseases with complex interactions

Fibrilación auricular y obesidad: dos enfermedades epidémicas con interacciones complejas

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ABSTRACT

Atrial fibrillation (AF) is a chronic degenerative and multifactorial disease with increasing prevalence and incidence that might even reach epidemic proportion, as with obesity. A highly prevalent problem worldwide. The combination of both conditions represents higher morbidity and mortality risks, and obesity is a risk factor for AF and worse outcomes of this complex arrhythmia. In the present work, we review the pathophysiological interactions between obesity and AF, the beneficial effects of obesity control on AF outcomes and the potentiation of better results with the current treatments for AF.

RESUMEN

La fibrilación auricular (FA) es una enfermedad crónica compleja, degenerativa y multifactorial cuya prevalencia e incidencia aumentan, de modo que puede considerarse una verdadera epidemia, como ocurre con la obesidad. La combinación de ambas enfermedades supone un mayor riesgo de morbilidad y mortalidad. La obesidad por sí misma es un factor de riesgo para la FA y se asocia con una peor evolución de esta compleja arritmia. En el presente trabajo, se revisan las interacciones fisiopatológicas entre obesidad y FA, así como los efectos positivos del control de la obesidad en la FA y la obtención de mejores resultados con las terapias disponibles en la actualidad para la arritmia.

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INTRODUCTION

Atrial fibrillation (AF), a degenerative, progressive, and multifactorial disease, is the most common persistent arrhythmia in adults and is considered an epidemic in this century. It is degenerative because prevalence and incidence increase with age, translating into an increase in mortality and a poor quality of life. The estimated prevalence of AF in adults is between 2 and 4%, and it will grow twofold due to population aging and a better capacity for arrhythmia diagnosis.[1] AF is a progressive disease and a risk factor for cerebrovascular accidents (CVA) in up to 25% of ischemic etiology.[2]

OBESITY AS A DISEASE AND RISK FACTOR FOR ATRIAL FIBRILLATION

Obesity prevalence has increased worldwide, and Mexico is not an exception: 46% of women between 30 and 59 years and 35% of men have obesity; this pathology is considered a modifiable risk factor for many cardiovascular diseases, including AF.[1,2] The Framingham heart study shows that for every unit of body mass index (BMI) increase, there is a 4% growth in the risk of AF regardless of the patient's sex.[3] Body mass index is still an independent risk factor with a linear relationship when adjusted to other risk factors or heart conditions.[4] The Women's Health Study, designed exclusively to associate

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gender with the risk of developing AF in 34,309 patients, followed by a mean time of 12.9 years, showed that such risk was directly proportional to BMI augmentation. At the same time, an increase in BMI of more than 25%, even in the short term, also increased the incidence of AF.[2,4]

Moreover, obesity is associated with cardiovascular risk factors that elevate the risk of AF, such as diabetes, hypertension, metabolic syndrome, cardiac failure, coronary artery disease, chronic disease, and obstructive sleep apnea (OSA).[1,5,6] The seep heart study showed that patients with respiratory problems related to OSA have a fourfold incidence of AF and non-sustained ventricular tachycardias.[5,6]

Obesity modifies hemodynamic regulation, neurohumoral, metabolic inflammatory, and autonomic system functions.[2,4,6,7] Changes in the hemodynamic regulation derived from obesity also include increased cardiac output due to increased systolic volume and left ventricular hypertrophy with diastolic dysfunction of several degrees. If this condition is sustained, increases in the end-diastolic pressure will lead to diastolic dysfunction and left atrium enlargement, causing high venous pressure, and retrograde pulmonary capillary pressure, exacerbating the clinical symptoms.[2,4,6,8]

The physiopathologic relationship between obesity and AF is complex and unclear since obesity is considered a proinflammatory systemic state related to adipokine dysregulation. In patients with a respiratory pathology such as OSA, the inflammation is aggravated by hypoventilation and secondary hypoxia, which will stimulate the liberation of more inflammatory cytokines such as the tumor necrosis factor-alpha, interleukin 1-beta and interleukin-6 among others.[2,4,8] Obesity and OSA could also increase the possibility of AF recurrence in patients submitted to an AF ablation procedure.[1]

Emphasis has been placed on the relevance of both pericardial fat and epicardial adipose tissue in the induction of the inflammatory immune response mediated by the paracrine action of the adipokines. Under this hormonal influence, the fat infiltration in the atrial myocardium and the myocardial remodeling can lead to significant fibrosis, more evident in the left atrium.[6,7] The inflammatory cytokines and chemokines could be responsible for the dysfunction of ion channels and atrial fibrosis, which will induce reentry circuits in AF.[2,6,7] Adipokines are bioactive proteins located and secreted predominantly in the adipose tissue. They participate in systemic mechanisms like energy and lipid metabolism, insulin sensitivity, and angiogenesis.[9] However, plenty of evidence suggests these molecules exist in various tissues, including the myocardium.[10] They act through different signaling pathways in many physiological processes, including cardiovascular function.[11]

Even though the mechanisms by which adipokines are involved in the development of atrial fibrillation have not been elucidated yet, several studies have addressed this issue by describing an association between anti-inflammatory and pro-inflammatory adipokines with the onset of AF.[12] Nevertheless, the results reported are scarce and contradictory. For instance, some authors stated no association between the anti-inflammatory adipokine adiponectin and the risk of stroke, whereas others reported the opposite. The same occurred with other adipokines like apelin, chemerin, and resistin; therefore, it is likely that the results reported in epidemiological studies would not suffice to implement adipokine-dysregulated levels as biomarkers for AF prevention.[13] Thus, combined clinical, epidemiological, and molecular approaches should be considered to improve AF outcomes.

On the other hand, it is common for obese people to present enlargement of the left atrium, specifically if the indexed volume of the body surface area evaluates the latter. Also, it is common to find adipose tissue infiltration of the atrial myocardium and anomalies in the systemic inflammatory response due to adipose tissue enlargement in abdominal and epicardial fat.[14]

At the cellular level, electromechanical atrial remodeling leads to a fragmentation of the endoplasmic reticulum, causing changes in protein folding and localization, especially those related to autonomic connections. Also, mitochondrial adaptations to impaired cellular homeostasis have been observed. In this context, it is known that mitochondria of metabolically stressed atrial tissue from both human and animal models present an increased production of reactive oxygen species. The latter and advanced glycation end products

lead to inflammation and the promotion of cardiovascular diseases, including diabetic cardiomyopathy and AF.[14] Therefore, cardiac chambers do not need to dilate or tension to increase in the parietal myocardium for AF to appear and perpetuate.

The use of direct anticoagulants in overweight or obese patients reduces the risk of suffering any systemic embolism myocardial infarction (MI), and pulmonary thromboembolism (PTE) (OR: 0.75; CI 95%: 0.66 a 0.84 and OR: 0.62; CI 95%: 0.54 to 0.70, respectively) as opposed to what happens in patients with a BMI less than 25 kg/m^2 body surface.[15] This phenomenon is known as the «obesity paradox». Obese patients could have a better prognosis than those with a normal BMI; however, no randomized controlled studies confirm this observation.[6,8,15] This phenomenon could result from better metabolic reserves, less cachexia, and increased mass and muscular tone. These changes could be due to the renin-angiotensin-aldosterone system's activation and an increased cytokine level with a protective effect against the cardiovascular drugs used in hypertension treatment, most prevalent in these subjects. Despite all these associations, the observation has yet to be reported within an observational cohort study or in studies with long-term follow-ups.[8,16]

Direct oral anticoagulants or the antagonists of vitamin K are indicated in patients with obesity and AF, just like they are recommended to all patients with arrhythmia, even if their BMI is more than 40-50 kg/m^2 BS. No antiplatelets are recommended in any patient with atrial fibrillation.[17-25]

EFFECTS OF WEIGHT LOSS

It has also been observed that weight loss is directly related to a diminished arrhythmic burden and improved symptoms.[26,27] The LEGACY study[28] showed that patients with AF that were able to reduce their corporal weight by more than 10% of their initial weight at the beginning of the study had six times more probability of being free of AF or other atrial arrhythmias in a five-year follow-up compared to patients that did not lose weight, or that had a weight reduction inferior than 3%.[2,8,28] In the REVERSE-AF study,[29] 88% of the patients with a sustained weight reduction of 10% of the basal body weight went from persistent AF to paroxistic or no AF at al. The same study found that 86% of the patients that could reduce their body weight were free of arrhythmias during the follow-up. Although this measure delays an ablation procedure, this should not be a factor in not performing or delaying pulmonary vein isolation in patients with an indication for the procedure. Despite these observational data, it has not been demonstrated that weight reduction in patients with AF diminishes the long-term risk of embolic events or other clinical adverse outcomes such as mortality, ictus, or hospitalization due to cardiac failure.[2,8]

As mentioned earlier, there seems to be a complex relationship between obesity and AF. The physiopathological mechanisms include many factors; however, the direct intervention of weight reduction positively affects the progression of the arrhythmia. This kind of intervention is low-cost, and the significant results reinforce the importance of preventing and controlling cardiovascular risk factors. Implementing public health policies in this regard should be more efficient in reaching more population sectors, thus reducing the health, social, and economic burdens of arrhythmias expected to be more prevalent soon.

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