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Review

The Implications of Obesity for Cardiac Arrhythmia Mechanisms and Management

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ABSTRACT

The ever-increasing prevalence of obesity poses a significant burden on the health care system with escalating socioeconomic consequences. At the individual level, obesity is well recognized to increase morbidity and mortality. Not only is obesity an established cardiovascular risk factor, it also increases the risk of sudden cardiac death and atrial fibrillation. Studies have shown that increased adiposity itself and the accompanying metabolic consequences of weight gain contribute to an abnormal arrhythmogenic substrate. In this review, we focus on the diverse mechanisms underlying cardiac arrhythmias related to obesity. In particular, we highlight the pathogenic role of adipose depots leading to increased atrial fibrillation and the effect of weight reduction in decreasing atrial fibrillation burden in obese individuals.

RÉSUMÉ

L'important fardeau que représente la constante croissance de la prévalence de l'obésité a des conséquences socioéconomiques de plus en plus grandes sur le système de soins de santé. Sur le plan individuel, il est bien reconnu que l'obésité augmente la morbidité et la mortalité. Non seulement il est établi que l'obésité est un facteur de risque cardiovasculaire, mais il est également reconnu qu'elle augmente le risque de mort cardiaque subite et de fibrillation auriculaire. Les études ont montré que l'augmentation de l'adiposité en soi et que les conséquences métaboliques qui accompagnent le gain de poids contribuent au substrat arythmogène anormal. Dans la présente revue, nous nous concentrons sur les divers mécanismes à l'origine des arythmies cardiaques liées à l'obésité. En particulier, nous soulignons le rôle pathogène des dépôts adipeux entraînant l'augmentation de la fibrillation auriculaire et l'effet de la réduction du poids sur la diminution du fardeau de la fibrillation auriculaire chez les individus obèses.

The prevalence of obesity is high with recent estimation at more than 1 of 3 adults and 1 of 7 youths affected.[1] Considering the pandemic nature of this problem, the medical costs of obesity are staggering.[2] Importantly, several longitudinal studies have demonstrated the association between obesity and cardiac dysrhythmias with increased risk of sudden cardiac death (SCD)[3] and atrial fibrillation (AF)[4,5] linked to increased adiposity. Historically, the propensity for cardiac arrhythmias in obesity was recognized as early as the fourth century BC when Hippocrates observed, "sudden death is more common in those who are naturally fat than in the lean." However, the mechanisms by which obesity could result in increased atrial and ventricular arrhythmias remain incompletely understood.

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The metabolic consequences of weight gain and the accompanying comorbid conditions often seen in obese individuals such as hypertension, arterial stiffness, diabetes, and sleep apnea, are also known independent contributors to adverse cardiac remodelling leading to increased arrhythmogenicity.[6-18] However, this review is focused on the specific effect of obesity on cardiac arrhythmia mechanisms and recent evidence for optimal management with weight reduction strategies.

Obesity and AF

Several population-based studies have demonstrated a robust relationship between obesity and AF.[4,5,14,19] Data from the Framingham cohort study have demonstrated a significant dose relationship with increased risk of developing AF with increasing severity of obesity.[4] This relationship holds true even after multivariate adjustment for other known risk factors with 3%-7% increased AF risk per unit increment of body mass index.[4,5,14,19] Specifically, the dilated left atria seen in obese subjects appear to be mechanistically important as the association between body mass index and AF was significantly weakened when adjustments were made for left atrial size in

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the Framingham study.[4] Left atrial dilatation and atrial dysfunction are known consequences of the cardiomyopathy due to obesity.[20] Indeed, earlier data have demonstrated a hazard ratio of 1.39 for developing AF per 5 mm increment in left atrial diameter.[21] More recently, left atrial dilatation has also been linked to AF recurrence and progression to chronic AF,[22,23] and left atrial dysfunction has been shown to increase the risk of new-onset AF.[24] Further, acute left atrial stretch in the setting of left ventricular (LV) diastolic dysfunction has been shown to be pivotal to AF promotion in an obese rat model with acute obstructive sleep apnea.[16]

The atrial remodelling as a result of obesity encompasses more than the anatomical and functional changes as described herein. Significant atrial electrical remodelling has also been identified from recent studies. Obese AF patients had shorter atrial and pulmonary vein effective refractory period compared with their normal weight counterparts.[25] Increased adiposity measured according to body mass index was found to be significantly associated with larger electrocardiographic P wave indices including P wave duration, PR interval and P wave terminal force, indicative of underlying atrial electrophysiologic remodelling.[26] Similarly, in an ovine model of diet-induced obesity, we have demonstrated atrial conduction slowing with increased conduction heterogeneity leading to increased AF inducibility.[27] Further, these electrical changes were seen in conjunction with increased atrial interstitial fibrosis, inflammation, and myocardial lipidosis.[27] The electrostructural abnormalities of increased interstitial fibrosis resulting in increased separation within and between muscle bundles are thought to interfere with electrical conduction thereby promoting atrial reentry and fibrillation.[28] Such changes have been featured in other established AF substrates of congestive heart failure, hypertension, and myocardial ischemia.[9,11,12,29-34] The complex signalling pathways underlying atrial fibrosis in obese hearts remain incompletely understood to involve at the very least, the transforming growth factor-β_1, connective tissue growth factor, and endothelin-1 system.[27]

Role of adipose depots and adipokines

Recent attention has focused on the increased epicardial adipose tissue in obese hearts and its association with AF. Increased posterior left atrial fat thickness or pericardial fat detected using computed tomography imaging has been shown to be independently associated with AF burden.[35,36] Similarly, pericardial fat determined using magnetic resonance imaging has also been shown to be associated with AF burden, severity, and AF recurrence after catheter ablation.[37] Of note, these associations were found to be independent of standard measures of adiposity such as body mass index or body surface area.[35-37] A noninvasive method for quantitation of atrial pericardial adipose tissue has recently been validated and will facilitate further studies.[38] The mechanisms by which pericardial fat leads to atrial remodelling remain incompletely understood. Recent evidence suggests a significant association between pericardial fat and atrial conduction abnormalities determined using electrocardiographic P-wave indices.[39] Further, epicardial fat is thought to contribute to atrial fibrosis via paracrine effects. Venteclef et al. have elegantly demonstrated that secretome from human epicardial adipose tissue could induce atrial fibrosis in a rat organoculture model.[40] The epicardial adipose tissue was rich in adipofibrokines including activin A, a member of the transforming growth factor beta 1 (TGF-β) superfamily, that was found to be responsible for the profibrotic effects in a paracrine-dependent fashion.[40] Moreover, infiltration of adipocytes into the atrial myocardium from the epicardial fat depot has been shown in human samples with increased pericellular fibrosis in its surround (Fig. 1).[41] Taken together, the altered 3-dimensional atrial architecture in obese hearts with epicardial adiposity, adipocyte infiltration into the myocardium, and the resultant increase in atrial fibrosis might contribute to conduction heterogeneity and anisotropy that promote a profibrillatory substrate of re-entry and endo-epicardial electrical dissociation and breakthrough.[42-44]

Animal and human studies have demonstrated that the expansion of adipose tissue with obesity is accompanied by inadequate capillarization, resulting in hypoxia.[45-48] Hypoxia of the adipose tissue has been shown to result in alteration of gene expression, with hypoxia-inducible factor 1α being the key transcriptional factor mediating adipose tissue fibrosis.[49] Adipocytes encased in fibrous tissue undergo necrosis and prompt infiltration by macrophages, neutrophils, and lymphocytes, leading to a proinflammatory microenvironment, with production and release of proinflammatory cytokines and alteration in adipokine levels. Obesity is associated with increased leptin and reduced adiponectin levels.[50,51] These alterations might also contribute to adverse atrial remodelling with increased atrial fibrogenesis and AF persistence.[52,53] In addition, in vitro studies on rabbit left atrial myocytes have demonstrated that leptin could acutely prolong action potential duration in an inhomogeneous manner that can be proarrhythmic, although a lower incidence of isoproterenol-induced delayed afterdepolarization was also seen.[54]

Role of proinflammatory cytokines, oxidative stress, and autonomic dysregulation

Obesity is associated with a proinflammatory state and increased oxidative stress.[55] Increased leukocyte count and various proinflammatory cytokines including C-reactive protein, interleukin 6, and tumour necrosis factor-α have been shown in obese subjects.[56,57] Several markers of systemic inflammation have been shown to be significantly associated with AF development in large cohort studies.[58,59] Although the arrhythmogenic mechanisms as a result of increased inflammation and oxidative stress are not fully understood, they are likely to involve alterations in ion channel properties, calcium handling, and homeostasis and atrial fibrosis.[27,60,61]

Obesity is also associated with autonomic nervous system dysfunction. Increased sympathetic activity and reduced vagal tone have been demonstrated in obese subjects with increased urinary norepinephrine excretion and alterations in heart rate variability measures.[62] The contributory role of the autonomic system has been demonstrated elegantly in an obese rat model with acute obstructive sleep apnea whereby autonomic blockade resulted in reduced AF inducibility.[16]

Obesity and SCD

Epidemiological studies suggest a significant association between SCD and obesity.[3,63,64] Recent data also indicate a greater prevalence of obesity with greater likelihood of ventricular arrhythmias in middle-aged sudden cardiac arrest victims