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ORIGINAL INVESTIGATIONS

Electrophysiological, Electroanatomical, and Structural Remodeling of the Atria as Consequences of Sustained Obesity

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ABSTRACT

BACKGROUND Obesity and atrial fibrillation (AF) are public health issues with significant consequences.

OBJECTIVES This study sought to delineate the development of global electrophysiological and structural substrate for AF in sustained obesity.

METHODS Ten sheep fed ad libitum calorie-dense diet to induce obesity over 36 weeks were maintained in this state for another 36 weeks; 10 lean sheep with carefully controlled weight served as controls. All sheep underwent electrophysiological and electroanatomic mapping; hemodynamic and imaging assessment (echocardiography and dual-energy x-ray absorptiometry); and histology and molecular evaluation. Evaluation included atrial voltage, conduction velocity (CV), and refractoriness (7 sites, 2 cycle lengths), vulnerability for AF, fatty infiltration, atrial fibrosis, and atrial transforming growth factor (TGF)-β1 expression.

RESULTS Compared with age-matched controls, chronically obese sheep demonstrated greater total body fat ($p < 0.001$); LA volume ($p < 0.001$); LA pressure ($p < 0.001$), and PA pressures ($p < 0.001$); reduced atrial CV (LA $p < 0.001$) with increased conduction heterogeneity ($p < 0.001$); increased fractionated electrograms ($p < 0.001$); decreased posterior LA voltage ($p < 0.001$) and increased voltage heterogeneity ($p < 0.001$); no change in the effective refractory period (ERP) ($p > 0.8$) or ERP heterogeneity ($p > 0.3$). Obesity was associated with more episodes ($p = 0.02$), prolongation ($p = 0.01$), and greater cumulative duration ($p = 0.02$) of AF. Epicardial fat infiltrated the posterior LA in the obese group ($p < 0.001$), consistent with reduced endocardial voltage in this region. Atrial fibrosis ($p = 0.03$) and TGF-β1 protein ($p = 0.002$) were increased in the obese group.

CONCLUSIONS Sustained obesity results in global biatrial endocardial remodeling characterized by LA enlargement, conduction abnormalities, fractionated electrograms, increased profibrotic TGF-β1 expression, interstitial atrial fibrosis, and increased propensity for AF. Obesity was associated with reduced posterior LA endocardial voltage and infiltration of contiguous posterior LA muscle by epicardial fat, representing a unique substrate for AF.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BP = blood pressure
CL = cycle length
CoV = coefficient of variation
CS = coronary sinus
ERP = effective refractory period
HE = hematoxylin and eosin
IQR = interquartile range
LA = left atrium/atrial
LAA = left atrial appendage
LV = left ventricular
OSA = obstructive sleep apnea
PA = pulmonary artery
RA = right atrium/atrial
TGF = transforming growth factor

Atrial fibrillation (AF) is an important health problem, with 2010 global estimates suggesting that it affects 33.5 million individuals (1). This prevalence is projected to increase 2.5-fold by 2050 (2). Emerging evidence suggests that aging alone does not account for the exponential rise in AF prevalence (2). It is in this setting that new risk factors, such as obesity, have been proposed as important contributors to this epidemic (3). Obesity is a rampant epidemic, with more than one-third of the population being overweight or obese. Analysis of population-based studies suggests that obesity is associated with long-term increased risk of AF, independent of other risk factors (4–6). In a meta-analysis by Wanahita et al. (7), there was a graded dose-response relationship between obesity and AF in the general population.

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The mechanisms by which obesity predisposes to AF are confounded by the coexistence of obstructive sleep apnea (OSA), hypertension, diabetes, and coronary artery disease, all well-established precursors for the development of AF. Using limited, open-chest, direct contact mapping, we have previously shown conduction slowing and atrial fibrosis with short-term weight gain in an ovine model (8). In the present study, we investigate the global endocardial electrophysiological, electroanatomic, and structural substrate with sustained obesity, a state more comparable with humans.

METHODS

The animal research ethics committees of the University of Adelaide and the South Australian Health and Medical Research Institute, Adelaide, Australia, which adhere to the National Health and Medical Research Council of Australia Guidelines for the Care and Use of Animals for Research Purposes, approved the study.

OBESE OVINE MODEL. A total of 10 sheep had obesity induced through a previously described protocol using an ad libitum regimen of hay and high-energy pellets (9). At baseline, healthy sheep were commenced on a high-calorie diet of energy-dense soybean oil (2.2%) and molasses-fortified grain and maintenance hay with weekly weight measurement. Excess voluntary intake was predominantly of grass alfalfa silage and hay. For the obese sheep, pellets were gradually introduced at 8% excess basal energy requirements, and rationed to ≥70% of total dry-matter intake. Blood samples were periodically collected to ensure electrolyte and acid-base homeostasis. The sheep gradually gained weight, reaching maximal obesity at 36 weeks and were subsequently maintained in this state for a further 36 weeks.

CONTROL GROUP. Ten age-matched sheep were maintained as controls at their baseline weight. To do this, high-quality hay was provided ad libitum, while energy-dense pellets were rationed at 0.75% of body weight. The nutritional content of food and housing conditions were identical for both groups, with only the amount of food intake varying.

STUDY PREPARATION. Animals were pre-acclimatized for at least 1 week before any surgery. Shorn weight was recorded immediately before surgery.

BODY COMPOSITION. Dual-energy x-ray absorptiometry scans were performed to determine total body fat in the animals.

TRANSTHORACIC ECHOCARDIOGRAPHY. An echocardiogram (Acuson Aspen, Siemens Healthcare, Malvern, Pennsylvania) was performed under general anesthesia before the electrophysiology study. The left atrial (LA) dimensions were measured in the

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