Obesity results in progressive atrial structural and electrical remodeling: Implications for atrial fibrillation

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BACKGROUND Obesity is associated with atrial fibrillation (AF); however, the mechanisms by which it induces AF are unknown.

OBJECTIVE To examine the effect of progressive weight gain on the substrate for AF.

METHODS Thirty sheep were studied at baseline, 4 months, and 8 months, following a high-calorie diet. Ten sheep were sampled at each time point for cardiac magnetic resonance imaging and hemodynamic studies. High-density multisite biatrial epicardial mapping was used to quantify effective refractory period, conduction velocity, and conduction heterogeneity index at 4 pacing cycle lengths and AF inducibility. Histology was performed for atrial fibrosis, inflammation, and intramyocardial lipidosis, and molecular analysis was performed for endothelin-A and -B receptors, endothelin-1 peptide, platelet-derived growth factor, transforming growth factor β1, and connective tissue growth factor.

RESULTS Increasing weight was associated with increasing left atrial volume ($P = .01$), fibrosis ($P = .02$), inflammatory infiltrates ($P = .01$), and lipidosis ($P = .02$). While there was no change in the effective refractory period ($P = .2$), there was a decrease in conduction velocity ($P < .001$), increase in conduction heterogeneity index ($P < .001$), and increase in inducible ($P = .001$) and spontaneous ($P = .001$) AF. There was an increase in atrial cardiomyocyte endothelin-A and -B receptors ($P = .001$) and endothelin-1 ($P = .03$) with an increase in adiposity. In association, there was a significant increase in atrial interstitial and cytoplasmic transforming growth factor β1 ($P = .02$) and platelet-derived growth factor ($P = .02$) levels.

CONCLUSIONS Obesity is associated with atrial electrostructural remodeling. With progressive obesity, there were changes in atrial size, conduction, histology, and expression of profibrotic mediators. These changes were associated with spontaneous and more persistent AF.

KEYWORDS Atrial fibrillation; Remodeling; Conduction velocity; Obesity; Fibrosis

ABBREVIATIONS **AF** = atrial fibrillation; **CHI** = conduction heterogeneity index; **CL** = cycle length; **CMRI** = cardiac magnetic resonance imaging; **CTGF** = connective tissue growth factor; **CV** = conduction velocity; **ERP** = effective refractory period; **ET** = endothelin; **ETA** = endothelin-A; **ETB** = endothelin-B; **H&E** = hematoxylin and eosin; **LA** = left atrial; **LAA** = left atrial appendage; **LAFW** = left atrial free wall; **LAP** = left atrial pressure; **MAP** = mean arterial pressure; **PDGF-BB** = platelet-derived growth factor; **RA** = right atrial; **RAA** = right atrial appendage; **RAFW** = right atrial free wall; **TGF-β1** = transforming growth factor β1

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Introduction

Obesity is recognized to be associated with the development of atrial fibrillation (AF) and has been proposed as a contributor to the expanding epidemic of this arrhythmia.[1,2] Atrial structural and electrical remodeling have been implicated in the AF substrate associated with many conditions predisposing to the development of this arrhythmia[3–6]; however, whether weight gain and obesity result in atrial remodeling is not known. Moreover, induction of this substrate along the adiposity spectrum of normal weight to obesity, and its relationship to hemodynamic disturbances, remains unknown. In this study, by using a sheep model of progressive weight gain, we aimed to characterize the atrial functional, structural, and electrophysiological changes accompanying increasing adiposity.

Methods

Animals

Thirty-six sheep (Merino Cross Wethers) were studied in accordance with guidelines outlined in the "Position of the American Heart Association on Research Animal Use," adopted in November 11, 1984. This study was approved by the Animal Ethics Committees of the University of Adelaide and SA Pathology, Adelaide, Australia.

Study protocol

Thirty animals underwent ad libitum feeding to induce obesity, as previously described.[7] At baseline, 4 months, and 8 months, 10 of the cohort were randomly selected for cardiac magnetic resonance imaging (CMRI) followed by open chest electrophysiology study. An additional 6 sheep were studied (3 at each of the 2 time points: 4 months and 8 months) as controls.

Ad libitum feeding obese ovine model

A previously characterized model of progressive weight gain, using an ad libitum regimen of hay and high-energy pellets, was used to induce progressive weight gain.[7] This model showed an approximate increase of 10 kg/month up to 36 weeks, after which weight gain reached a plateau. In brief, at baseline, 30 healthy animals were commenced on a high-calorie diet of unlimited supply of high-energy soybean oil (2.2%), 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 $\geq$70% of the total dry matter intake. Blood samples were periodically collected to ensure electrolyte, glucose, and acid-base homeostasis. To maintain the 6 controls at their baseline weight, hay was distributed for maintenance while high-energy pellets were rationed at 0.75% of live weight daily to maintain weight tightly between 50 and 60 kg. Nutritional content of food and housing conditions were identical between both groups, but only the amount was varied. Shorn weight was recorded immediately prior to surgery. Study outline is illustrated in Figure 1.

Cardiac magnetic resonance imaging

Chamber volumes were measured by using CMRI (Siemens Sonata 1.5 Telsa, MR Imaging Systems, Siemens Medical Solutions, Erlangen, Germany) with 6-mm slices through the atria and 10-mm slices through the ventricles without interslice gaps. Animals were securely placed in the dorsal recumbent position for scanning. Mechanical ventilation was maintained, facilitating electrocardiogram-gated image acquisition with periodic breath holding. Analyses were performed offline by blinded operators by using the proprietary software QMass MR (Medis medical imaging systems, Leiden, The Netherlands). Chamber size, ventricular mass, and pericardial fat volumes were measured by using previously described methods.[8]

Animal anesthesia

Intravenous sodium thiopentone (15–20 mg/kg) was used for induction before endotracheal intubation. Isoflurane in oxygen (2%–4%) was used for maintenance. Invasive arterial blood pressure, heart rate, pulse oximetry, end-tidal CO_2, and temperature were monitored continuously.

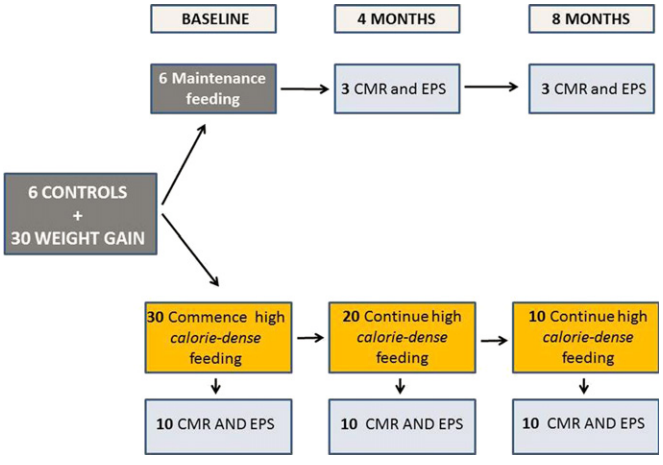

Figure 1 Study outline. CMR = cardiac magnetic resonance; EPS = electrophysiology study.