Determinants of atrial fibrillation in an animal model of obesity and acute obstructive sleep apnea

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BACKGROUND Obesity and obstructive sleep apnea (OSA) are risk factors for atrial fibrillation (AF), but the underlying mechanisms are poorly understood.

OBJECTIVE The purpose of this study was to assess the mechanisms underlying AF promotion by obesity and OSA in rat models.

METHODS Zucker obese rats (ORs) and lean rats (LRs) were intubated and ventilated with air and 2% isoflurane. OSA was mimicked by stopping the ventilator and closing the airway for 40 seconds. For nonobstructive control periods, the protocol was repeated with an open airway. Fifteen seconds after apnea onset, AF susceptibility was tested with 6 atrial burst pacing cycles (25 Hz, 3 seconds, 1-second intercycle pauses).

RESULTS AF was not inducible in ORs or LRs at baseline or in nonobstructive control periods. AF was induced in 24 of 28 ORs (85.7%) vs 5 of 18 LRs (27.8%) during obstructive apnea ($P < .001$). Negative intrathoracic pressure generation (esophageal pressure monitoring) was substantial during obstructive apnea. Echocardiography showed left ventricular hypertrophy with diastolic dysfunction in ORs. Obstructive apnea caused acute left atrial (LA) dilation, increasing LA diameter significantly more in ORs than in LRs. To clarify AF mechanisms, 24 AF-inducible ORs were divided into 4 groups: saline (n = 5), pharmacologic autonomic blockade (n = 7), respiratory muscle paralysis with rocuronium (n = 6), and inferior vena cava (IVC) balloon occlusion to unload the LA (n = 6). Balloon catheter–induced IVC occlusion prevented LA distension during obstructive apnea, leading to 83.3% AF prevention ($P < .05$). Rocuronium also was protective (66.7%), but autonomic blockade had smaller effects (42.9% prevention).

CONCLUSION Obesity and acute obstructive apnea interacted to promote AF in this model. Forced inspiration–induced acute LA distension related to diastolic dysfunction may be an important component of the arrhythmogenic substrate for AF during OSA episodes in obese patients.

KEYWORDS Atrial fibrillation; Left atrial distension; Negative intrathoracic pressure; Obesity; Obstructive sleep apnea

ABBREVIATIONS **AF** = atrial fibrillation; **AV** = atrioventricular; **D** = diastolic; **ERP** = effective refractory period; **IVC** = inferior vena cava; **IVRT** = isovolumic relaxation time; **IVRTc** = corrected isovolumic relaxation time; **LA** = left atrium; **LAD** = left atrial dimension; **LV** = left ventricle; **LV-AWT** = left ventricular anterior wall thickness; **LVDd** = left ventricular dimension at end-diastole; **LVDs** = left ventricular dimension at end-systole; **LVEDP** = left ventricular end-diastolic pressure; **LV-FS** = left ventricular fractional shortening; **LV-PWT** = left ventricular posterior wall thickness; **OSA** = obstructive sleep apnea; **PAC** = premature atrial contraction; **PVF** = pulmonary venous flow; **RA** = right atrium; **RV-AWT** = right ventricular anterior wall thickness; **S** = systolic; **S/D ratio** = systolic/diastolic flow ratio

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Introduction

A number of studies have demonstrated that obesity increases the risk of atrial fibrillation (AF).[1–4] Obesity commonly clusters with the metabolic syndrome, diabetes, hypertension, and obstructive sleep apnea (OSA), all of which may contribute to the development of AF. OSA is particularly associated with obesity,[5] with OSA present in more than 40% of obese patients.[6] Obesity and OSA are associated with multiple abnormalities implicated in the pathogenesis of AF, including hypoxia,[7] negative intrathoracic pressure leading to increased atrial wall stress, sympathovagal imbalance,[8,9] left ventricular (LV) diastolic dysfunction,[10,11] systemic inflammation,[12] and increased intravascular volume.[13] OSA induces deeply negative intrathoracic pressure,[14] increases venous return, impairs LV filling, and diminishes stroke volume. Strongly negative intrathoracic pressures activate intrathoracic baroreceptors, inducing autonomic reflex responses that promote AF.[9] AF onset tends to occur during sleep apnea episodes, suggesting that episodes of OSA acutely enhance the risk of AF.[15]

The pathogenesis of AF in obesity is uncertain. Although studies in animal models mimicking sleep apnea have been

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performed,[9,16] none have assessed potential interactions with obesity. This study was designed to assess the mechanisms underlying AF promotion in obesity and OSA by utilizing Zucker obese rats, which are widely used in experimental studies of metabolic syndrome and obesity.[17]

Methods

Animal model

All experimental protocols were approved by the local animal research ethics committee and conformed with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (Publication No. 85–23, revised 1996). Twenty-week-old male Zucker obese rats (n = 38) were studied, with age-matched Zucker lean rats (n = 26) used as controls (all rats from Charles River, Wilmington, MA, USA). Rats were intubated and ventilated with 2.0% isoflurane in room air. Octapolar electrode catheters (1.9F; Scisense FTS-1913A-1018, London, Ontario, Canada) were introduced into the right atrium (RA) through the right internal jugular vein. A surface ECG (lead II) and intracardiac electrograms were recorded and digitized (IOX 2.516 A/D-converter, EMKA Technologies, Paris, France) for monitoring and subsequent offline analysis. A 3F pressure transducer catheter (Scisense P catherter-3F) was inserted into the esophagus for evaluation of intrathoracic pressure.[18] Three-way stopcocks were attached to the endotracheal tube to control the airway.

Electrophysiologic study

Programmed RA stimulation was performed in subsets of animals (12 rats/group) at a cycle length of 150 ms (pulse width 2 ms, 2× threshold current) to determine the RA and atrioventricular (AV) conducting system effective refractory period (ERP). Atrial and AV conducting system ERPs were defined as the longest S1-S2 coupling interval that failed to generate a propagated beat. To assess atrial tachyarrhythmia inducibility, 25-Hz burst pacing (pulse width 2 ms, 4× threshold current) was applied for 3 seconds, with six 3-second burst cycles separated by 1-second intervals. AF was defined as a rapid (>800 bpm) irregular atrial rhythm, and AF inducibility was defined as AF lasting for at least 5 seconds immediately following the 6-burst cycle protocol. If AF was induced after fewer than 6 burst pacing cycles, burst pacing was suspended so as not to interfere with the evolution of AF. Wenckebach cycle length was defined by failure of 1:1 AV conduction as determined by RA pacing with decremental steps of 5 ms. Sinus node recovery time was determined by 30-second RA pacing with a cycle length of 150 ms.

OSA simulation

OSA was mimicked by turning off the ventilator and closing the airway for 40 seconds. Fifteen seconds after ventilator arrest, the same AF induction protocol was applied during apnea (Figure 1A). A nonobstructive control intervention was also studied, in which the same protocol was repeated in each rat during ventilatory arrest with an open airway (Figure 1B).

Hemodynamic study

A 2F pressure transducer catheter (Scisense P catheter-RAT) was introduced into the LV of subsets of animals (6 rats/group) through the left internal carotid artery. Systolic, diastolic, and LV end-diastolic pressures were determined during apnea. LV catheter position was adjusted to avoid catheter-induced arrhythmia during apneic episodes. In

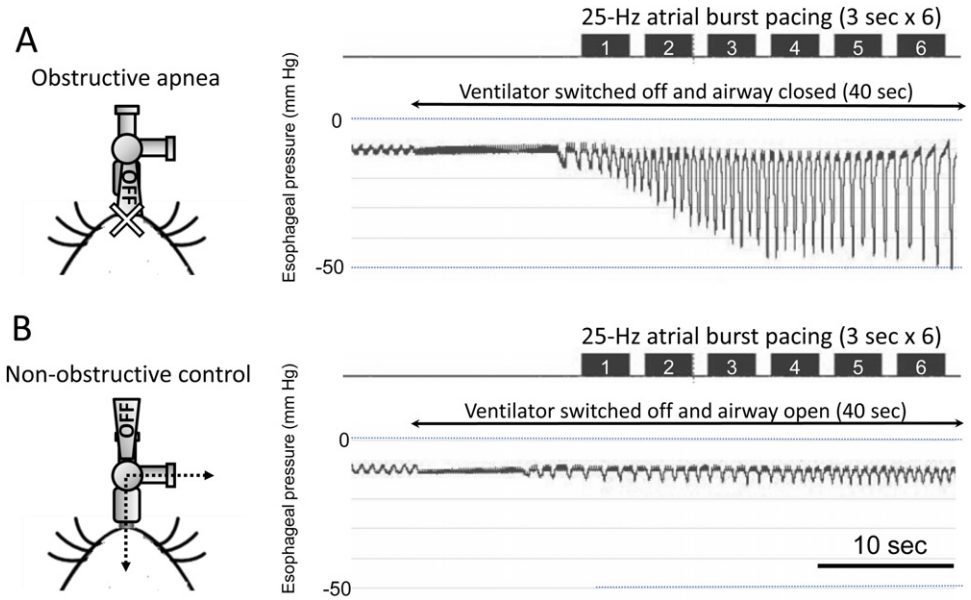

Figure 1 Schematic of experimental protocol. **A:** Obstructive apnea was induced by stopping the ventilator at end-expiration and closing the airway for 40 seconds. Forced inspiration against a closed airway generated large negative intrathoracic pressures. **B:** To obtain a nonobstructive control period, the same protocol was repeated during ventilatory arrest with an open airway. During both apnea paradigms, 25 Hz-burst pacing (2-ms pulse width, 3-second duration) was begun 15 seconds after apnea onset as 6 burst cycles separated by 1-second intervals.