Reflections from the Book of the Dead: Weighing the Impact of Epicardial Fat on Atrial Fibrillation Vulnerability

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The ancient Egyptians wrote in the Book of the Dead, that all deeds in life, whether good or bad, remain in our hearts. As such, when a person died their spirit traveled to the underworld to be judged by the weight of their heart by Osiris, the Lord of the Underworld. A heavy heart reflected a life of poor choices and deeds and as a consequence the heart was thrown into the jaws of Amenti, a God with the face of a crocodile, and their soul would cease to exist. If their heart was light, a reflection of good deeds and choices, they then lived in the eternal paradise of the Field of Reeds.(1)

Atrial fibrillation (AF) is the most common sustained clinical arrhythmia and is increasingly across the world in both developed and developing countries.(2) The increase in AF has been attributed to aging of the population, higher rates of traditional risk factors for AF, and also, as of now, additional unknown risk factors. Obesity is commonplace in electrophysiology practices and as illustrated by the median body mass index (BMI) of 30 kg/m^2 reported in the CABANA trial, the level at which obesity is defined, a common comorbid condition in patients with AF.(3)

In an analysis of 626,603 people, incident AF risk was increased by 19% (OR: 1.19, 95% CI: 1.13 to 1.26) for every 5-unit BMI increase in case-control studies.(4) The mechanisms underlying the AF-obesity association are not fully understood and on the surface are multifactorial and often synergistic. Amongst these mechanisms is the contribution to AF risk related to the presence and extent of pericardial and epicardial adipose tissue (EAT).

EAT is a marker of obesity, in particular central or visceral obesity, more so than BMI alone.(5) In a meta-analysis of 38 studies, the EAT was 7.5 $\pm$ 0.1 mm in thickness in the patients with metabolic syndrome compared to 4.0 $\pm$ 0.1 mm in controls. EAT also correlates with a higher systolic blood pressure, fasting blood glucose, and triglycerides.(5) Recently it has been discovered the EAT is metabolically active and directly influences the adjacent myocardium through inflammatory, paracrine, and vasocrine signaling that results in lower myocardial bipolar voltage and electrogram fractionation; substrate associated with AF genesis and

maintenance.(6) In a supportive ovine model, obese sheep had increased voltage heterogeneity, more frequent and durable episodes of AF, more atrial fibrosis, and reduced endocardial voltage in regions with epicardial fat infiltration.(7)

Despite these recent observations regarding the negative influence of EAT on myocardial substrate that becomes vulnerable to arrhythmia, questions such as how AF is triggered and how the arrhythmia is maintained as a consequence to the presence and severity of EAT remain unknown. In order to answer these questions, Otsuka and colleagues from the University of Nihon created a novel canine model with groups exposed to obesity, obesity with rapid triggered atrial activity from pacing, and a combination of both.(8) The model consisted of 3 year old health beagle dogs and obesity was stimulated through feeding them with a high-fat diet (standard diet plus 235 g/day of white rice and 400 g/day of high-calorie dog food [2210 kcal/day]) for at least 20 weeks. In a subset of animals, right atrial pacing was performed to stimulate AF induction and triggering during the last 6 weeks of the dietary period, whether in the standard diet group or in the high-fat diet group. Pacing was performed from two sites within the right atrium and to prevent tachy-mediated heart failure, an AV node ablation was performed with subsequent dependent VVI pacing. All animals underwent a baseline and terminal electrophysiology study and bipolar voltage mapping.

There were several interesting findings that implicate both obesity and right atrial pacing as mediators of AF vulnerability through similar pathways. For example, gene expression mediators of inflammation and fibrosis, fibronectin, collagen I, collagen III, and TGF-β1 mRNA expression levels were significantly increased in the obese, obese with right atrial pacing, and right atrial pacing groups compared to controls with the largest relative differences in the two groups with right atrial pacing.

Unlike the prior ovine study(7), in this model, there were no observed regional differences in bipolar voltages after comparing findings from 5 discrete left atrial sites and 3 venoatrial junctions amongst the different groups, although the obese paced group had significantly lower sampled voltages throughout followed by the right atrial pacing nonobese group. These findings suggest more of a generalized myopathic process related to pacing that may be accelerated or further mediated by the presence of obesity. This myopathic process may have been driven in part by higher left atrial pressures that were more common in obese animals compared to nonobese animals.

Animals exposed to right atrial pacing, both obese and not obese, demonstrated shorter effective refractory periods in the pulmonary veins. However, the obese animals at the terminal study were 3-4 times more likely to sustain AF, a finding that suggests obesity within this model was contributing to the substrate and maintenance of properties of AF.

The finding most interesting to me was uncovered in histologic analysis. The extent of EAT differed significantly between the 4 groups: control 93 (41–179) μm; right atrial pacing not obese 249 (178–355) μm; obese 233 (136–329) μm; right atrial pacing obese; 334 (243–550) μm, p=0.006. In addition, the percent of fatty infiltration in the myocardium differed significantly: control 7.3 (0.7–17.1)%; right atrial pacing not obese 29.3 (21.4–47.6)%; obese 27.9 (12.5–31.7)%; right atrial pacing obese; 43.1 (38.6–48.6)%, P<0.001. It was not surprising based upon prior studies that obesity influenced EAT and EAT infiltration into the myocardium. However, pacing alone resulted in greater EAT accumulation and infiltration than diet alone and this maladaptive response to the adverse electrical stimulus was significantly augmented by the presence of obesity. The pathways that leads to EAT and myocardial infiltration of fat, that results in a higher risk of AF, may serve as therapeutic opportunities to lower risk in people with AF triggers with and without obesity. The development and infiltration of EAT may also explain why outcomes with rhythm control are much better when used early in the course of AF, before atrial structural changes become nonreversible.(9)

There are some limitations to consider with this study. Importantly, it was unclear if the obesity model truly created a metabolic syndrome that would impact myocardial function and health. Leptin is synthesized and secreted into the circulation largely by adipocytes and was similar in all groups, despite higher insulin levels in the obese groups. Higher levels of leptin are associated with worse outcomes in patients with coronary artery disease, left ventricular hypertrophy, and heart failure.(10) It is possible that a more chronic model of

obesity beyond 20 weeks in previously healthy animals may have elicited a greater adverse influence of obesity alone. Next, there were relatively few animals, 20 total, with multiple comparisons of 4 discrete treatment groups (5 in each), which increases the likelihood of a type 2 statistical error. As a consequence, additional studies are needed to reproduce these findings and expand on their insights. Despite these limitations, the authors are to be congratulated on developing this model and providing a comprehensive analysis to improve our mechanistic understanding underlying the contribution of obesity and AF incidence and progression.

Circling back to the beginning, do our deeds impact the "weight" of our hearts. Or in other words, how much of obesity is related to lifestyle choices versus genetic and as a consequence how much of EAT is modifiable? In a study of 1608 white people studied over 25 years, polygenetic risk scores predicted the BMI at 25 years in 13.6% of the population.(11) Within this study, fitness improved model prediction and predicted BMI at 25 years in 18.1% of the population. The BMI at enrollment in early adulthood was the strongest predictor of BMI 25 years later. With this study in mind, our choices to maintain fitness influence risk of obesity similar to, or perhaps slightly more, than our genetics. Second, these choices to pursue a fit life need to be considered early as the adopted lifestyles that convey risk tend to remain over decades of life. Perhaps electrophysiologists have learned what the Egyptians knew centuries before, that our hearts convey a lifetime of experiences and if we are not careful, some future misery along the way.

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