Abstract: P314

Modifications of atrial refractoriness produced in an experimental rabbit model of diet-induced metabolic syndrome

Authors:
OJ Arias-Mutis\textsuperscript{1}, CJ Calvo\textsuperscript{2}, A Bizy\textsuperscript{2}, L Such-Miquel\textsuperscript{2}, C Soler\textsuperscript{2}, L Such\textsuperscript{2}, SV Pandit\textsuperscript{3}, A Alberola\textsuperscript{2}, FJ Chorro\textsuperscript{4}, M Zarzoso\textsuperscript{2}, \textsuperscript{1}CIBERCV - Valencia - Spain, \textsuperscript{2}University of Valencia - Valencia - Spain, \textsuperscript{3}University of Michigan - Ann Arbor - United States of America, \textsuperscript{4}Research Foundation Hospital of Valencia (INCLIVA) - Valencia - Spain,

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Introduction: Metabolic syndrome (MetS) describes an association between diabetes, hypertension, obesity and dyslipidemia, and it has been linked with a higher prevalence of cardiovascular disease, arrhythmogenesis and sudden cardiac death. Indeed, it has been reported that obese and diabetic patients have increased risk for atrial fibrillation (AF), but the underlying mechanisms are not well understood.

Purpose: Our aim was to investigate the atrial structural and electrophysiological remodeling in a diet-induced experimental model of MetS and its potential arrhythmogenic mechanisms.

Methods: Male NZW rabbits were randomly assigned to a control (n=12) or a MetS group (n=13), fed during 28 weeks with high-fat (10% hydrogenated coconut oil and 5% lard) and high-sucrose (15% dissolved in water) diet. Transthoracic echocardiography and electrocardiography were performed before diet and at weeks 14 and 28. Then, hearts were isolated and perfused in a Langendorff system. Pacing and recording electrodes were positioned on the left atria. Refractoriness was assessed using an atrial extrastimulus test with different pacing cycle lengths (PCL). Left atrial effective (LAERP) and functional (LAFRP) refractory periods were measured. Samples from left (LA) and right atria (RA) were taken and mRNA expression levels for Nav1.5, Cav1.2, Kir2.1, Kv4.2, KChIP2 and KvLQT1 were examined by qRT-PCR. Computer simulations including adjusted conductance regulations under MetS remodelling were explored to assess independent effects on action potential duration and frequency under reentrant-AF. A mixed model ANOVA and unpaired t-test were used for statistical analysis (p<0.05).

Results: Left atrial diameter and P wave duration increased in MetS animals at week 28 (10.8±1.01 vs. 9.1±0.6 mm and 45±9 vs. 33±5 ms, respectively; p<0.05). In isolated heart, we found a decrease in both LAERP and LAFRP in all the PCL studied (Panel A). The mRNA expression levels for KvLQT1 increased in both LA and RA, KChIP2 in LA (Panel B) and Kir2.1 tended to increase in RA (p=0.07). Nav1.5, Cav1.2, and Kv4.2 remained unaltered in both atria. Computer simulations of MetS remodeling showed an abbreviation in APD in both atria (12.4% and 16.8%, in RA and LA), with increased reentrant frequencies in AF (6.5% and 8.3%, in RA and LA), exacerbated under IK1 upregulation (Panel C), further increasing atrial vulnerability.

Conclusion: High-fat and high-sucrose diet administration during 28 weeks produced a dilation of LA and increased P wave duration. In isolated heart, we observed a shortening of LA refractoriness, which could be explained in part by an upregulation of outward potassium channels, mainly KvLQT1 and KChIP2, as shown in computer simulations. The decrease of LA refractoriness could be related to the increased susceptibility for AF in MetS.
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1 CIBERCV - Valencia - Spain, 2 University of Valencia - Valencia - Spain, 3 University of Michigan - Ann Arbor - United States of America, 4 Research Foundation Hospital of Valencia (INCLIVA) - Valencia - Spain

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Panel C: Computer simulations of MetS remodeling showed an abbreviation in APD in both atria (12.4% and 16.8%, in RA and LA), with increased reentrant frequencies in AF (6.5% and 8.3%, in RA and LA), exacerbated under IK1 upregulation (Panel C), further increasing atrial vulnerability.