ABSTRACTS FOR ORAL PRESENTATION, SESSION 1, HRC2014

THE BRUGADA SYNDROME AND CARDIOMYOPATHY: ALTERED COLLAGEN AND GAP JUNCTION EXPRESSION

H. Raju[1], S.V. de Noronha[1], S. Rothery[2], L. Robinson[1], M. Papadakis[1], S. Sharma[1], M.N. Sheppard[1], and E.R. Behr[1]

[1]St George's University, London; and [2]Imperial College, London

Background: Brugada syndrome (BrS) is considered an inherited arrhythmia syndrome, though it may represent a concealed cardiomyopathy confined to the right ventricular outflow tract (RVOT). We aimed to ascertain fibrosis and gap junction expression in ventricular myocardium following sudden cardiac death (SCD) due to BrS.
Methods: The BrS cohort consisted of 6 cases of unexplained SCD referred for specialist whole heart autopsy whose family were diagnosed with BrS. Comparisons were made to matched homograft control hearts (n = 6) and cases of arrhythmogenic right ventricular cardiomyopathy (ARVC, n = 5). Morphometric evaluation of collagen and fat content of left (LV) and right (RV) ventricles and RVOT by picrosirius red-staining was undertaken. Gap junction expression was assessed by Connexin43 (Cx43) immunostaining in the RVOT.
Results: Collagen in controls was predominantly perivascular in long fine fibres and diffuse reticular interstitial networks. Interstitial long collagen strands were thickened in BrS, with evidence of epicardial patchy replacement fibrosis. ARVC was characterised by both interstitial and dense patchy replacement fibrosis. Maximal collagen content, indicative of fibrosis, was present in the RVOT ($p = 0.003$) and epicardium ($p = 0.001$) in all three disease groups, with RV more fibrosed than LV ($p = 0.020$). ARVC cases exhibited the most fibrosis ($p = 0.001$), while BrS cases were significantly more fibrosed than controls (OR 1.42; $p = 0.024$). No significant difference in fat content was observed between BrS and controls ($p = 0.133$).

BrS cases showed a reduced Cx43 signal in comparison to controls (OR 0.59; $p = 0.001$), which remained significant after adjusting for collagen content (Figure). However, lateralisation and dispersion of Cx43 over the cellular surface was seen in both control and BrS sections. In ARVC, Cx43 signal was severely reduced in comparison to BrS (OR 0.61; $p = 0.002$).
Discussion: BrS associates with generalised ventricular myocardial fibrosis and reduced RVOT gap junction expression in comparison with controls, with ARVC demonstrating similar but more severe abnormalities. Thus, BrS may represent a disease of myocardial architecture, with baseline properties of the RVOT predisposing it to more severe fibrosis. We speculate that myocyte electrical uncoupling indicated by gap junction abnormalities and changes in conduction related to fibrosis confer arrhythmic risk.

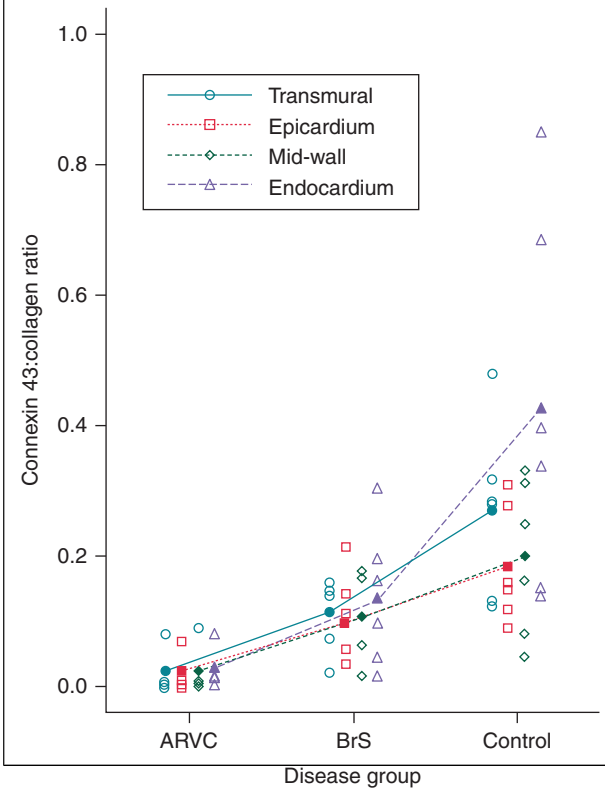

Figure Scatterplot of Cx43:collagen ratio in RVOT by myocardial zone (filled data points = mean) demonstrating significant differences between ARVC, BrS and Control cohorts, but no difference from epi- to endo-cardium.