G46 Fatty Versus Fibrofatty Involvement of the Myocardium in Sudden Death and Heart Failure

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After attending this presentation, attendees will recognize the pattern of pathologic and histologic findings as correlated to clinical information from cases within the spectrum of fatty cardiomyopathy including arrhythmogenic right ventricular cardiomyopathy.

This presentation will impact the forensic science community by reviewing clinical and pathological data as well as associated histology for sudden cardiac death cases from the spectrum of fatty cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Forensic and cardiovascular pathologists, as well as other forensic scientists, may find this information useful for comparison with observations from their home institutions and practices.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disease characterized by fibrofatty replacement of myocardium in the right ventricle (RV) and to lesser degree in the left ventricle. ARVC is commonly associated with sudden death and heart failure. Isolated infiltration of the RV by fat alone is also believed to be associated with sudden death. However, the ARVC phenotype versus that characterized by isolated fatty infiltration alone have an unclear separation. Such lack of clarity makes pathological evaluation of sudden death in these circumstances very challenging. While genetic testing for mutations in genes known to be associated with ARVC would aid in rendering a diagnosis, that approach is not practical in everyday pathology practice. One other possible strategy in better delineating phenotypic variation might be immunohistochemical staining and quantitative evaluation of proteins related to genetic mutations underlying some ARVC phenotypes.

Purpose and Approach: In this study, heart case materials from autopsy (8) and cardiac transplantation (2) from patients with ARVC and fatty infiltration of the RV are characterized. Each case was accessioned in the iCAPTURE Cardiovascular (CV) Biobank at St. Paul's Hospital/University of British Columbia and each case was referred to a cardiovascular pathologist at the CV Biobank for assessment. Under approved ethics protocols, patient data were obtained from medical records or referring pathologists. The CV Biobank, a research and educational tool, was established in 1982 and includes cardiovascular tissue specimens from surgery and autopsy, along with their accompanying annotations and data held in a secure database.

Methods & Results: The Ten sets of case materials were archived between 1993 and 2008. All hearts were assessed for their macroscopic and microscopic features with confirmation by at least two observers. The specimens were found to fit into one of two patterns. Nearly two- thirds demonstrated **fibrofatty** (6 male, age = 17-36 years) replacement of the RV myocardium, while about a 1/3 showed a pattern of predominantly **fatty** replacement (2 male, 2 female; age = 15-64 years). Within the fatty replacement group, individuals died during non- strenuous activity and at rest. In this group, one individual had a history of fainting and clinical intervention for arrhythmia and one patient had a history of anorexia and bulimia. In the fibrofatty replacement, group patients died following non-strenuous activity, during strenuous activity and at rest. This group of patients included one individual with documented familial ventricular tachycardia for which he received treatment, one patient with dilated cardiomyopathy and mitral valve regurgitation, and one individual with sudden death of a brother due to an unspecified "aneurysm". Quantitative computer-assisted morphometric analysis confirmed two pathological phenotypes, fibrofatty and fatty. Of interest, the distribution and extent of involvement differed substantially between fibrofatty and fatty patterns, with changes being more extreme and widely distributed in the fibrofatty group, while localized to the anterolateral apex and lateral base in the fatty category. None of the hearts studied had a notable cellular inflammatory element. Further, immunohistochemical staining was performed on all heart cases for desmosomal protein plakoglobin, a protein that links adhesion molecules at the intercalated disk to the cytoskeleton and is thought to aid in the evaluation of ARVC.

Summary and Conclusion: Fibrofatty replacement of the RV, characteristic of ARVC, and fatty infiltration of the RV alone are distinctive phenotypes in the setting of sudden cardiac death and heart failure. The distinctly different extent and distribution of involvement between the two morphological patterns supports the concept that they represent different disease processes. Further, preliminary quantitative

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analysis of immunohistochemical staining for plakoglobin suggests that such staining may aid in the assessment and distinction of these two conditions.

ARVC/ Fatty Cardiomyopathy, Cardiovascular Pathology, Sudden Cardiac Death

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