and in 24/207 pleomorphic lobular carcinomas (11.6%). All 83 tubular carcinomas were ER positive and HER2/neu negative. HER2/neu was positive in 2/129 mucinous carcinomas; these tumors had grade 2 nuclei. HER2/neu positivity correlated with high tumour grade; 1.98% in low grade tumours vs. 11.69% in intermediate grade and 20% in high-grade tumours ($p<0.001$).

Conclusions: Our results confirm that the rate of HER2/neu positivity is less than 20%. There is strong correlation with tumour grade. Special histologic types associated with low tumour grade and positive hormonal status are almost always negative for Her2/neu over-expression. Clinical follow-up of this large cohort will be added to further enhance the value of this database; as well the large number of cases allows for an opportunity to examine molecular markers in this cohort, particularly in special histologic types.

Cardiovascular

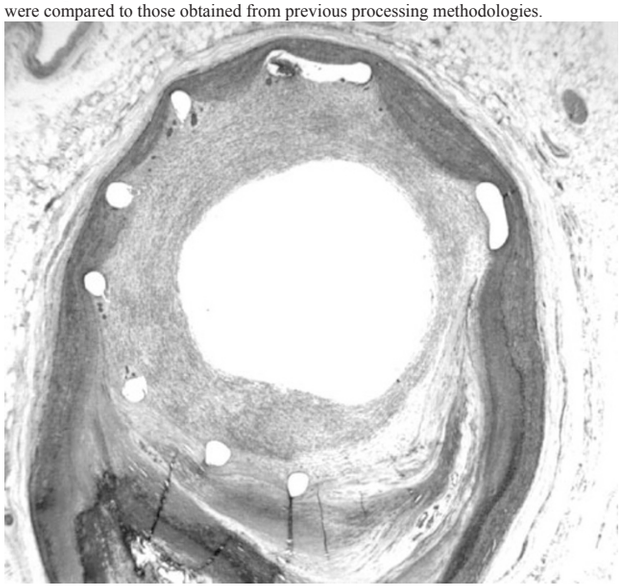
335 Electrolytic Method for Processing Coronary Arteries Containing Stents

SH Bradshaw, JP Veinot, LA Kennedy, DF Dexter. Queen's University, Kingston, ON, Canada; The Ottawa Hospital, Ottawa, ON, Canada.

Background: Due to its hardness, sectioning through a stent using conventional methods causes significant damage to and/or loss of native morphology of the underlying tissue. Current specialized methods exist for making thick and thin sections through metal implants, however they are expensive, time consuming, and require a high degree of operator skill. In addition, cutting artifacts and undesirably thick microscopic sections are common. A novel electrochemical method is described and tested, which addresses these difficulties.

Design: A positive voltage was attached to a stent imbedded in formalin fixed tissue, which was then suspended in a grounded electrolytic solution. The stent dissolved over a time interval of 5 to 30 minutes, after which the tissue was sectioned. Residual small metallic fragments were removed as required. The resulting sections were processed according to standard histological techniques.

Results: Sixteen stents were dissolved using this electrolytic process. These included 316L stainless steel and Cobalt-Chromium core materials, as well as drug eluting and bare metal stents. The underlying tissue was preserved, and histological sections obtained, including H&E, Movat (figure 1), and several immunohistochemical stains. The sections were compared to those obtained from previous processing methodologies.



Conclusions: The electrolytic stent removal process was applied successfully to a broad range of stents, representing the majority of stent designs encountered in practice. Histological sections obtained compared favorably to those obtained with previous processing methodologies. Other improvements over previous methods include low cost, short processing time, short operator time, low skill level required, increased consistency of results, and compact size.

336 Arrhythmogenic Cardiomyopathy: A Biventricular Disease with Predilection for African-Americans

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Background: The ventricular distribution of arrhythmogenic cardiomyopathy (AC) in sudden death has not been studied in detail, especially in relation to racial and exertional status. There have been few immunohistochemical studies of sarcomeric related proteins.

Design: Fifty cases of sudden cardiac death with the diagnosis of AC were retrospectively studied. Distribution of disease as determined grossly and microscopically was correlated with activity at time of death, race, and presence of inflammation. AC was defined as subepicardial or right ventricular fibrofatty change surrounding altered cardiac myocytes with disordered myofilaments and vacuolated cytoplasm. Racial and gender incidence was compared to 500 cases of sudden cardiac death due to other causes seen in consultation during the same time period. Immunohistochemical stains for connexin-43, desmin, alpha tubulin, sarcomeric actin were performed on AC cases.

Results: There were 23 whites (44%), 25 blacks (50%), and 2 Asians (6%) with AC; the proportion of blacks was greater than the non-AC sudden deaths (50% vs. 34%, p=.01). Death was exertional in 29 cases (58%) vs. 5% for non-AC SD (p<.0001) and there were 7 women (14%) vs. 26% for non-AC sudden death (p=.05). Extent of disease was predominantly right ventricular in 6 (12%, age 25±5 years), biventricular in 25 (50%, age 36±3 years), and left ventricular (ALVC) in 19 (38%, age 37±3 years), with some overlap in 38 (76%). There was no difference in proportion of blacks by ventricular distribution (p>.9). RV dilatation was present in 22 (44%) and aneurysms were present in 2 (4%); there was no correlation between RV dilatation and race or exertion. The proportion of exertional deaths was greatest in right ventricular AC (ARVC, 83%) followed by ALVC (58%) and biventricular (50%, p=0.2). Inflammation was present in 44% of biventricular AC, vs. 74% of LVNC and 83% of ARVC (p=.05). Immunohistochemical staining for sarcomeric proteins (sarcomeric actin), desmin, alpha tubulin and connexin-43 demonstrated disruption of myofilaments in areas of scarring, but no abnormalities in areas remote from fibrofatty or inflammatory infiltrates.

Conclusions: Arrhythmogenic cardiomyopathy, when presenting with sudden death, is usually biventricular, with inflammation more predominant in RV involvement. There may be a predilection for African-Americans. Sarcomeric structure appears normal in non-involved areas.

337 Molecular Autopsy of Sudden Cardiac Death: Preliminary Experience of the Northeast Italy Juvenile Sudden Death Registry

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Background: Molecular genetic screening is currently employed in the clinical diagnostic track of inherited cardiovascular diseases to identify disease-causing mutations. More recently, these techniques have been also applied to sudden death (SD) autopsies which remain unexplained after a thorough post-mortem investigation or in those with inherited cardiomyopathies. The aim of this study was to perform a genetic screening of known disease-causing genes involved in catecholaminergic polymorphic ventricular tachycardia (CPVT) or arrhythmogenic right ventricular cardiomyopathy (ARVC).

Design: Ten cases of juvenile SD (all males, age range 16-35 yrs) from the Veneto Region Registry were investigated. Genetic screening was performed for cardiac ryanodine receptor (RyR2) and calsequestrin (CASQ2) genes in two cases with structural normal heart, and for plakophilin-2 (PKP2), desmoplakin (DSP), desmoglein-2 (DSG2), desmocollin-2 (DSC2) and plakoglobin (JUP) genes in eight cases with ARVC. In five cases the investigation was conducted directly in the proband who died suddenly on frozen autoptic EDTA-blood (3), on frozen tissue (1) or on paraffin-embedded tissue (1). The other five cases were studied indirectly by screening EDTA-blood samples of parents.

Results: The autoptic paraffin embedded tissue was inadequate, whereas frozen autoptic EDTA- blood and frozen tissue were suitable for genetic investigation. Pathogenic gene mutations were identified in five SD cases: in 2 cases in the autopsy probands (one ARVC~DSG2-H790Y, one unexplained SD with structurally normal heart~RyR2-A2387P), and in the other 3 cases indirectly in the parents (all ARVC: PKP2-G59X, DSP-c.1686+1 C>T, DSG2-V56M). The mutation identified indirectly was discovered in the blood of the mother in two cases and of the father in one. None of these mutation was detected in a 100 genomics DNA (200 chromosomes) from unrelated healthy control subjects from Venetian population.

Conclusions: Molecular autopsy is mandatory on SD cases with structural normal heart as well as in those with inherited structural cardiomyopathies, since it can be potentially life-saving in terms of management and prevention of those left behind. Moreover, it is mandatory that the standard SD autopsy includes archiving either EDTA-preserved blood or frozen tissue to allow postmortem genetic testing.

338 Vascular Fibrosis Correlates with Hypertension, Kidney Function, and Diabetes in a Wide Range of Vascular Tissues

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Background: Chronic disease states are thought to affect vascular fibrosis in atherosclerosis-prone, large caliber blood vessels. We compared the degree of fibrosis in these vessels to fibrosis in other medium-sized atherosclerosis resistant vessels from the same subjects to determine if vascular fibrosis is a global phenomenon.

Design: Eight unique blood vessels (carotid, coronary, dorsalis pedis, iliac, internal mammary, mesenteric, pulmonary and renal arteries) were harvested from 100 subjects undergoing autopsy, generating 17 vascular tissue microarrays (TMAs). Slides cut from TMA blocks were stained with Masson's trichrome, and automated image analysis methods were used to quantify fibrosis in these vessels. Clinical and sociodemographic variables from the subjects were evaluated relative to the amount of fibrosis present in the tunica media and tunica intima using correlation and t-tests.

Results: In 7 of the 8 studied vessels, the percentage of fibrosis in the tunica media was associated with a clinical history of hypertension (overall $p < 0.001$, t-test). Only the pulmonary artery, which is not subject to systemic pressures, did not associate with hypertension. Also, for any given subject, poor renal function (estimated glomerular filtration rate < 30 ml/min/1.73 m²; $p < 0.001$) and a history of diabetes ($p = 0.008$) was associated with an overall increase in medial fibrosis. The age, sex, ethnicity, and smoking history of a subject showed no correlation with the degree of fibrosis in any vessel. Media tunica fibrosis was strongly correlated among all vessels within a given subject ($r = 0.24$ to 0.72; $p < 0.03$).

Conclusions: This study is the first to compare the extent of fibrosis in eight distinct blood vessels collected from the same subjects. We confirmed that hypertension, attenuated kidney function and diabetes are risk factors for medial fibrosis in atherosclerosis-prone vessels, and identified new associations in smaller atherosclerosis-resistant vessels. We

demonstrated that medial vascular fibrosis is a global process within a given subject, as demonstrated by strong correlations among vessels within a given subject. Finally, a lack of correlation between age and medial fibrosis supports the hypothesis that vessels age as a result of chronic disease, independent of chronological age. These findings advance our understanding of the role of chronic disease in vascular fibrosis.

339 Incidence of Sudden Cardiac Death in Sport in England

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Background: Sudden death in healthy individuals engaged in regular sport is a rare but devastating phenomenon and is usually associated with previously undetected cardiovascular disease. We report for the first time the characteristics of a large series of sudden cardiac deaths (SCD) that occurred in England.

Design: Retrospective study of individuals engaged in sporting activity and who had a sudden cardiac death.

Results: 118 cases (6.6%) of SCD related to sport or with a regular history of sport were selected from a database of 1800 cases. The age range was 7 to 59 years (mean age, 27.9 ± 12.5) with the majority of deaths occurring in the younger age group (75%). Males predominated (113, 96%) with only 5 female deaths (4%) mainly in younger age group. Twenty patients (17%) showed a family history of cardiovascular disease and/or family history of SCD. Fifteen (13%) had a personal history of cardiac anomalies, whilst 21 (18%) had a personal history of other diseases including: 3 cases (3%) of insulin dependent diabetes mellitus, 11 cases (9%) of asthma and 3 cases (3%) of epilepsy. Thirty-three patients (28%) displayed pre-mortem symptoms with syncope, shortness of breath and feeling unwell being the dominant features. Seven cases (6%) were athletes at a professional or semi-professional level, 6 being footballers and one a professional cyclist. Four (3%) were in the armed forces. Eighty-two percent of the remaining cases were amateur athletes with a regular participation in sport activity. The top three sports associated with the greatest number of SCD were football with 44 subjects (37%) followed by running with 24 (20%) and rugby with 11 (9%). The table below summarises our final diagnoses.

Diagnoses	≤ 35	> 35	Total	% cohort
Cardiomyopathy	49	24	73	62%
Left ventricular hypertrophy (with fibrosis)	19 (3)	8 (6)	27 (9)	23% (8%)
Arrhythmogenic right ventricular cardiomyopathy	9	7	16	13%
Hypertrophic cardiomyopathy	11	2	13	11%
Idiopathic fibrosis	6	1	7	6%
undetermined CM	1	0	1	1%
Morphologically normal heart	26	1	27	23%
Coronary artery pathology	7	4	11	9%
anomalous coronary artery	6	0	6	5%
atherosclerosis	0	3	3	3%
coronary "spasm"	1	0	1	1%
coronary dissection	0	1	1	1%
Other cardiac pathology	7	0	7	6%
myocarditis	3	0	3	3%
valvular disease	2	0	2	2%
complex congenital heart disease	1	0	1	1%
sickle-cell crisis	1	0	1	1%

Conclusions: Sudden death in sports is rare. The main cardiac causes are cardiomyopathies, with LVH often associated with fibrosis, ARVC and HCM predominating. The presence of normal hearts in a significant number points to channelopathies being important in sport deaths. Screening of athletes should be undertaken to avoid these deaths.

340 Myocardial Inflammatory Infiltrate in the Hearts of Valve Donors

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Background: The histological evaluation of hearts used as valvular homograft is crucial to evaluate the donor's viability for heart valve homograft use, allowing the tissue bank to validate the graft. In the course of the routine evaluation of these hearts we observed by chance the appearance of unspecific inflammatory infiltrates, leading us to study a series of cases in order to establish their main characteristics, the differential diagnosis, its prevalence and relationship with the donor's main features.

Design: A prospective histological evaluation of 133 hearts accepted as valvular homograft was performed. In each case, five representative samples of myocardium were obtained, being the microscopic sections stained with H&E and examined for the presence, type (lymphocytes, neutrophils or both), density (graded semi quantitatively from 1+ to 4+, being the grade 4+ the case where the maximal density was observed) and extent of inflammatory cells (percentage of total area occupied by the infiltrate). The presence of myocyte necrosis foci was also evaluated and highlighted immunohistohemically with the antibody against C9. Donor's main characteristics were obtained in each case.

Results: Sixteen cases showed any type of inflammatory infiltrates not related to myocardial infarction or other known causes and most of them had lymphocytes as predominant cell type. In 7 cases the infiltrate was composed exclusively of lymphocytes, while in 2 there were neutrophils. The 7 remaining cases presented an admixture of lymphocytes and neutrophils. Myocardial inflammation was more frequently seen in brain death donors when compared to the other groups. When an echocardiography study was available, more than 80% of cases with inflammation showed myocardial dysfunction (very low ejection fraction and wall hypokinesia). Foci of myonecrosis were detected in 4 cases in association with lymphocytic infiltrates.

Conclusions: In the routine evaluation of hearts used as valvular homograft we can find inflammatory infiltrates in the myocardium, manly composed of lymphocytes and associated, in a minor proportion, with foci of myonecrosis. This finding should not be mistaken for a myocarditis, since this would preclude the use of the valvular homograft. Moreover, they could be the morphological expression of the well-recognized sympathetic storm secondary to the brain death situation.

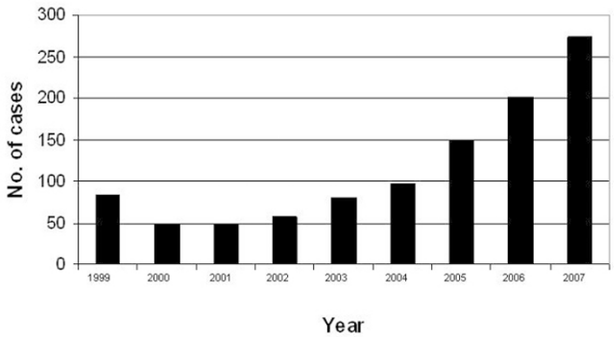
341 Setting up of a Pathology Laboratory To Investigate Sudden Cardiac Death. Results from First Year of CRY Centre for Cardiac Pathology

K Hault, SV de Noronha, MN Sheppard. Royal Brompton Hospital, Imperial College, London, United Kingdom.

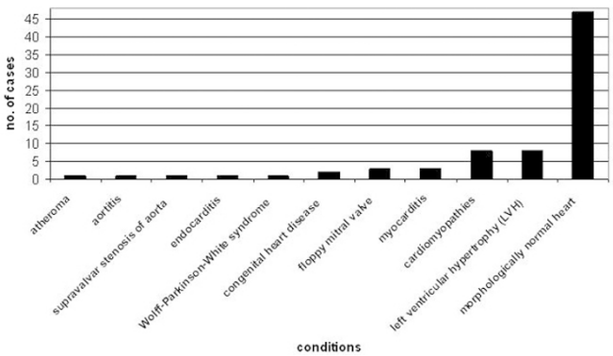
Background: Most sudden cardiac deaths (SCD) are due to ischemic heart disease. In the young it is due to inherited cardiac disease such as cardiomyopathy. Since 1992, The Royal Brompton Hospital has been a referral centre for SCD in the United Kingdom. As a result of this work, a charity called Cardiac Risk in the Young (CRY) helped us set up a unit specifically to investigate the cardiac pathology of these sudden deaths in order to help families with obtaining a specific diagnosis of the cause of death and refer them for cardiac screening.

Design: Retrospective study of hearts in sudden death with detailed histological analysis.

Results: Our referral pattern yearly has increased to 250 hearts per year (see figure below).



Our turn around time for issuing a report is 2 weeks from the receiving of the heart. The diagnosis includes mainly normal heart indicating that channelopathies are very important in the cause of young sudden deaths. Idiopathic left ventricular cardiomyopathy as well as cardiomyopathies come next with hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy predominating. Other causes are shown in chart below.



Conclusions: Families and the public are becoming aware of sudden cardiac death and wish to obtain a rapid and specific cause of the death. As a result of the establishment of the CRY Cardiac Pathology Unit, we are able to provide this rapid service and help families come to terms with a very traumatic event and assist with family screening. This is the first such unit in the world providing this service.

342 True Monckeberg-Type Calcification of Temporal Arteries: A Rare Pattern Associated with End-Stage Renal Disease

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Background: Three patterns of calcification of medium-sized arteries have been described: intimal calcification associated with atherosclerotic plaques, Monckeberg-type medial calcification, and a distinct pattern limited to the internal elastic lamina (IEL) which has been shown to be associated with increasing age. The high reported incidence of Monckeberg medial calcific sclerosis diagnosed at our institution prompted a review of the distribution of calcification in a series of biopsies from patients suspected to have temporal arteritis.

Design: 94 temporal arteries biopsied from 1998 to 2008 were reviewed, and qualitative and quantitative analysis of the histomorphology of the specimens containing calcification was performed. Qualitative data included intimal hyperplasia, medial calcification, arteritis, and IEL calcification (linear or nodular pattern with subclassification as nodular intimal or nodular medial). Quantitative data was calculated using ImageJ and included area of mineralization, intimal and medial area, and minimum and maximum intimal and medial thickness.

Results: 25 biopsies with mineralization (age range 47 to 89 years) were reviewed. IEL calcification was present in 24 cases including our only 2 cases of active giant cell arteritis. IEL calcification was linear in 13 and nodular in 11 cases. Nodular calcification involved the intima in 4 cases and the media in 7 cases. Calcification affected from 0.06% to 85% of the total (intimal + medial) area. There was no correlation between age and % of calcification. True medial calcification of Monckeberg-type was noted in 2 cases. Both patients were diabetic with end-stage renal disease on dialysis.
Conclusions: Calcification is common in temporal arteries biopsied for clinical suspicion of arteritis. The most common pattern is linear calcification of the IEL, which is not related to healed arteritis and may co-exist with active arteritis (2/2 cases). Atrophy of the media is seen with nodular calcification with medial extension. True Monckeberg medial calcific sclerosis is a separate and uncommon pattern of calcification in temporal arteries and is associated with end-stage renal disease/dialysis. Pathologists need to be aware of the different patterns of calcification and their clinicopathologic associations.

343 Obesity and Sudden Cardiac Death. Does a Specific Obesity Cardiomyopathy Exist? A Study of Predominantly Non-Ischaemic Causes of Sudden Death

AM Plonczak, SV de Noronha, MN Sheppard. Royal Brompton Hospital, Imperial College, London, United Kingdom.
Background: Obesity is a major health concern in the modern world and it is associated with an increased risk of sudden cardiac death.
Design: We investigated the cardiac pathology in 57 cases with history of sudden death and with BMI above 30.
Results: Sex and age (26F: 31M, average age =38) was equally distributed in the cohort. Morphologically normal hearts predominated (46%) followed by cardiomyopathies (37%) and coronary artery disease (11%). In those with normal hearts younger patients predominated (70%). In the cardiomyopathy group, idiopathic left ventricle hypertrophy with or without fibrosis (LVH) was the most common diagnosis (71%), followed by hypertrophic cardiomyopathy (HCM) (14%) . There was 1 case of dilated cardiomyopathy (DCM), 1 of arrhythmogenic right ventricular cardiomyopathy (ARVC) and 1 of idiopathic fibrosis (IF). Fatty infiltration of the right ventricle was present in 23 cases (40%), featuring in 52% of normal hearts, 50% of hearts with coronary artery disease (CAD) and 29% of hearts with cardiomyopathy.
Conclusions: Normal heart and idiopathic LVH with or without fibrosis are the main non-coronary causes of sudden death in obese young subjects in this study. Fatty infiltration of the right ventricle is also prominent in obesity. The incidence of possible channelopathies and obesity hypertrophy needs further investigation in this group with family screening. Further studies will compare with sudden cardiac death in non obese subjects.

344 Migration of Vascular Progenitor to Intimal Hyperplasia in Transplant Arteriosclerosis Is Mediated by Monocyte Chemoattractant Protein-1

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Background: Transplant arteriosclerosis is the major factor of late organ dysfunction after transplantation that involves migration of vascular progenitor cells. This process results in a progressive narrowing of the vessel lumen partly, due to a healing reaction in the intima. The aim of this study was to evaluate migration of tissue progenitor cells in transplant arteriosclerosis.
Design: To assess the clinical importance and mechanism of this infiltration, 124 myocardial biopsies from patients who received hearts from opposite-sex donors were examined for host-derived smooth muscle cells (SMCs) and inflammation. Clinical and demographic information were obtained from the patients' medical records.
Results: Host-derived SMCs accounted for 3.35 ± 2.3% of cells in arterioles (range, 0.08%–12.51%). The accumulation of host-derived SMCs was associated with an increased number of leukocytes in the allografts. Linear regression analysis showed an associated between an increased number of SMCs and the rejection grade (mean, 1.41 ± 1.03, p = 0.034) and the number of leukocytes (19.1 ± 12.7 *[per 20 high power field]*, p = 0.01).The study was followed by transplantation of aorta from female F344 to male Lewis rats and collected at different time points after transplantation. Migration and activation of host-derived SMCs and cells from surrounding tissue were analyzed by immunohistochemistry and real-time polymerase chain reaction (PCR) for the SRY gene. The structures of vessels were analyzed by immunohistochemistry and electron microscopy. Moreover micro DNA assays were performed and reveal potential role of MCP1, SDF-1, RANTES and IP10 in transplant vasculopathy. The role of these factors was further analyzed in vitro and in vivo with focus on stimulation of migration of vascular progenitor. The study indicated that MCP-1 is involved in migration of vascular progenitor in transplant vasculopathy.
Conclusions: The host derive SMCs are an important source of cells that form the intimal lesion. The MCP-1 is potent chemokine for recruitment of vascular progenitor cells in the development of transplant vascular arteriosclerosis.

345 Glycogen Storage Mimicking Arrhytmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

ER Rodriguez, CD Tan. Cleveland Clinic, Cleveland, OH.
Background: Glycogen storage in the heart can occur when the AMP-dependent protein kinase subunit γ2 (PRKAG2) gene is mutated. These patients commonly present with hypertrophic cardiomyopathy and diverse types of arrhythmias, including: preexcitation (Wolff-Parkinson-White syndrome; WPW), atrial fibrillation, and progressive atrioventricular block. In contrast arrhythmogenic right ventricluar dysplasia/cardiomyopathy (ARVD/C) is a disease that affects primarily the right ventricle, producing marked thinning of its free wall. This thinning of the wall shows adipose tissue infiltration and fibrosis which replace the cardiac muscle. These patients present with multiple arrhytmias or sudden death.
Design: A database of clinical features and results of pathologic examination reports was reviewed for the period January 1, 2006 to September 11, 2008. A total of 180 heart transplants were performed during this period. Age, gender and final pathologic diagnoses of hypertrophic cardiomyopathy (HCM) or ARVD/C were included in this study.
Results: Eight of 180 patients were identified as having HCM and/or ARVD/C. There were 3 males and 5 females. The average age was 49 years. Six patients had clinical diagnosis of HCM, 3 of which were proven histologically. The other 3 showed marked vacuolation of myocytes with sarcoplasmic eosinophilic inclusions which stained positive with PAS and showed excess glycogen on electron microscopy. Two patients had clinical diagnosis of ARVD, one of which showed marked hypertrophy of the left ventrcle and vacuolation of myocytes as described above. Thus a total of 4 patients showed glycogen storage, 2 of these 4 had mutations in the PRKAG2 gene. In addition, these two latter patients showed "paper thin" translucent right ventricular free walls and right ventricular outflow tract with loss of myocytes and fibro-fatty infiltration, confirmed by microscopic examination. Furthermore, these same 2 patients also had clinical histories of arrhytmias. There was only 1 patient with isolated ARVD/C by pathologic and clinical criteria.
Conclusions: This is the first report with clinico-pathologic and genetic confirmation of PRKAG2 glycogen storage mimicking ARVD/C. Glycogen storage disease is known to mimic hypertrophic cardiomyopathy. This study shows that glycogen storage diseease secondary to PRKAG2 mutation can mimic ARVD/C both, clinically and morphologically.

346 Mitogen-Activated Protein Kinases and Regulation of Mitochondrial Biogenesis in Human Cardiomyopathies

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Background: The most critical regulators of myocardial mitochondrial biogenesis are and its coactivator However, the upstream signaling pathways involved in PPARa/PGC-1a complex activation are still unknown. The aim of our study was to evaluate the role of mitogen-activated protein kinases (MAPK) ERK1/2, JNK and p-38 in cardiac mitochondrial biogenesis.
Design: Activation of MAPK was detected by the Bioplex suspension array system on left ventricular samples from control hearts (n=2) and recipient explanted hearts with either a) mitochondrial cardiomyopathies (MIC) due to the m.4300A>G substitution in the mt-tRNA^{Ile} gene (n=3) or b) heart failure resulting from other aetiologies (n = 5). PGC1a gene expression was evaluated in the same samples by real-time PCR.
Results: In MIC hearts, we show marked mitochondrial proliferation and significant increase in the expression of PGC1a (15-fold as compared to controls); these were associated with increased phosphorylation of p-38 and JNK, but not of ERK1/2. In contrast, PGC1a was down-regulated in failing hearts due to other aetiologies whilst ERK1/2, along with p-38 and JNK were strongly activated.
Conclusions: We show that MIC hearts are characterized by a specific pattern of MAPK phosphorylation. Besides the well known effect of p38 on PGC1a induction, inhibition of ERK1/2 seems necessary for mitochondrial biogenesis in heart.

347 Non-Atherosclerotic Coronary Artery Pathology Responsible for Sudden Cardiac Death

MN Sheppard, SF Hill. Royal Brompton Hospital, Imperial College, London, United Kingdom.
Background: Most sudden cardiac deaths (SCD) are due to ischemic heart disease. The concept of non-atherosclerotic coronary artery pathology in sudden death has not been given the attention it deserves. We sought to determine the incidence of this entity and raise awareness amongst cardiologists and pathologists alike. Since 1992, the Royal Brompton Hospital has been a referral centre for SCD in the United Kingdom. We have established a database of 1,800 SCD hearts.
Design: Retrospective study of hearts with non-atherosclerotic coronary artery causes of sudden death with detailed histological analysis.
Results: Fifty (2.7%) of the 1,800 cases of SCD were caused by non-atherosclerotic coronary pathology (31 men (62%) and 19 women (38%, age range [8 weeks-71 years]). Twenty- four of the 50 cases had anomalous coronary arteries (48%); eight cases had coronary artery dissection (16%); six cases had coronary artery vasculitis (12%); six cases had coronary artery spasm (12%); three cases had idiopathic arterial calcification of infancy (6%); two cases had fibromuscular dysplasia (4%) and one case had a benign tumour occluding the left coronary ostium (2%). Twenty of the 50 patients (40%) were documented to have experienced symptoms such as syncope, chest pain on exertion or breathlessness prior to their SCD. Twelve of the patients (24%) died during or immediately after physical exertion.
Conclusions: Non-atherosclerotic coronary pathology can cause sudden death in all age groups particularly younger, male patients. Cardiologists need to be aware of these entities and investigate any patient who has cardiac symptoms especially with exertion.

348 Ascending Aortic Aneurysms and Dissections: Histopathology and Genetic Testing

CD Tan, ER Rodriguez. Cleveland Clinic, Cleveland, OH.
Background: Ascending aortic aneurysms and/or dissections occurring at a young age are often associated with inheritable connective tissue disorders. Genetic testing for mutations in fibrillin (FBN1), transforming growth factor beta receptors I (TGFBR1)

and II (TGFBR2) is clinically available for the diagnosis of connective tissue disorders. Marfan syndrome (MFS) is caused by mutations in FBN1 and TGFBR2, while Loeys-Dietz syndrome (LDS) is due to mutations in TGFBR1 or 2.
Design: A total of 223 ascending aortic resections from patients aged 60 or less were accessioned between April 2007 to Aug 2008 and their histopathology results were tabulated. Referral pattern to clinical geneticists and results of genetic testing were reviewed from the medical records in this cohort of patients.
Results: Histopathologic examination showed aortic dissection in 52 patients (23%), cystic medial degeneration (CMD) in 45 (20%), increase in mucopolysaccharide content of the media without elastic fragmentation in 85 (38%), normal aorta in 15 (7%) and atherosclerosis in only 26 (12%). Of these 223 patients, 24 (11%) patients with either aortic dissection or CMD were referred to clinical genetics for evaluation. Five patients met the clinical criteria for MFS and diagnosis confirmed with mutations in FBN1. Nineteen patients did not meet criteria for MFS or LDS and were tested for TGFBR1 and 2; in addition, 4 patients also had FBN1 testing. One patient each were found to have mutation in TGFBR1, TGFBR2 and FBN1. The common clinical findings in these 3 patients are dilation of the ascending aorta, high-arched palate and translucent velvety skin. The patient with TGFBR1 mutation (c.1136T>C) is a 40 year old female with aortic dilatation and CMD on histology. The second patient with TGFBR2 mutation (c.914T>A) had thoracoabdominal aortic dissection at age 52 and found to have an enlarged aortic root. There was moderate increase of mucopolysaccharide material in the aorta but not CMD. Likewise, the 43 year old female with FBN1 mutation (c.2714G>A) did not show CMD in the aortic specimen. Conversely, 16 patients with mild to severe CMD did not have mutations in TGFBR genes.
Conclusions: In this retrospective analysis of patients with ascending aortic aneurysm or dissection, mutations were found in 15% of patients evaluated by a clinical geneticist. Phenotypic expression overlaps in patients with FBN1, TGFBR1 and 2 mutations. CMD is a nonspecific finding in ascending aortic aneurysms and dissections and is not always present in those with inheritable connective tissue disorders.

349 Isolated Vasculitis of the Female Genital Tract

CD Tan, J Hernandez-Rodriguez, GS Hoffman, ER Rodriguez. Cleveland Clinic, Cleveland, OH.
Background: Vasculitis involving the female genital tract is rare. This can be an isolated manifestation or part of a systemic disease. Diagnosis requires clinicopathologic correlation and appropriate clinical testing to rule out systemic involvement.
Design: Surgical pathology files were reviewed from 1992 to 2007 to identify cases of vasculitis involving the female reproductive system. Electronic medical records were utilized to determine the presence or absence of systemic disease with a minimum follow-up period of 6 months.
Results: There were 14 cases identified from a total of 9,846 hysterectomies with or without salpingo-oophorectomies over a 16-year period for an incidence of 0.14%. Five patients were excluded because of a lack of adequate follow-up data. Nine patients were found with isolated vasculitis after a median follow-up of 48 monhts. These patients range in age from 46 to 76 years. Symptoms were localized and related to vaginal bleeding or pelvic mass. Four of these patients had concurrent malignancies, 3 with endometrial carcinoma and 1 with ovarian carcinoma. The most common associated benign lesion was leiomyoma. The cervix accounted for the most frequent site of involvement (78%), either alone in 5 patients or in combination with the uterine corpus in 2 patients. One patient had vasculitis in the mesovarium. The most common histologic pattern is that of a necrotizing vasculitis involving medium-sized muscular-type arteries demonstrated in 7 patients (78%). The lesions are typically segmental with fibrinoid necrosis. The predominant inflammatory infiltrates are lymphocytes that can be admixed with neutrophils and rarely eosinophils. In contrast to systemic polyarteritis nodosa, inflammatory lesions are generally found in the same stage. One patient had lymphocytic vasculitis without fibrinoid necrosis and another patient showed granulomatous vasculitis. None of these 9 patients received medical treatment after the diagnosis of vasculitis.
Conclusions: Vasculitis of the female genital tract is rare and most often an incidental finding that is limited to the cervix. In majority of cases, these are isolated vasculitis. Histologically, these cannot be distinguished from systemic vasculitides. There is absence of systemic symptoms at the time of diagnosis. Patients do not require systemic therapy.

350 Diagnosis and Typing of Cardiac Amyloidosis in Routine Clinical Specimens by Mass Spectrometry Based Proteomic Analysis

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Background: Cardiac amyloidosis is a frequent cause of restrictive cardiomyopathy and, if untreated, leads to cardiac failure and death. Treatment strategies target the underlying pathogenesis and often involve high risk approaches such as organ transplantation. Therefore accurate typing of amyloid is of great clinical significance. Unfortunately, immunohistochemistry (IHC), currently used for typing amyloidosis, is problematic due to non-specific staining in approximately half of the cases. Here, we describe a novel mass spectrometry based proteomic approach which can type amyloidosis with high sensitivity and specificity and overcome many of the problems associated with IHC.
Design: We studied 56 cases of paraffin embedded cardiac biopsies involved by amyloidosis and 4 cases of normal cardiac biopsies. Congo red positive amyloid plaques were laser microdissected, trypsin digested, and analyzed by nano-flow liquid chromatography electrospray tandem MS (LC-MS/MS). The resulting LC-MS/MS data was correlated to theoretical fragmentation patterns of tryptic peptide sequences from the Swissprot database using Scaffold. Peptide identifications were accepted if established at greater than 90.0% probability and protein identifications were accepted if established at greater than 90.0% probability and contained at least 2 identified spectra. The identified proteins were examined for the presence or absence of amyloid related peptides. IHC for immunoglobulin kappa (IGK) and lambda (IGL) light chains, transthyretin (TTR), serum amyloid A (SAA) was performed in 52 cases.
Results: In 53/56 cases studied, LC MS/MS identified the presence of a single amyloidogenic protein. 35 cases showed a peptide profile consistent with TTR, 15 cases with IGL, 2 cases IGK and 1 case with SAA. No amyloidogenic peptides were identified in normal cardiac stroma or muscle. Of the cases where IHC was performed, staining was considered to be diagnostic in 19 cases and inconclusive in 33 cases. In each case, the IHC confirmed LC MS/MS findings. In those cases where the IHC was non-contributory, additional clinical and pathological information supported the amyloid type assigned by mass spectrometry.
Conclusions: LC-MS/MS proteomic analysis provides a highly specific and sensitive method for diagnosis and classification of amyloidosis in cardiac biopsy specimens. The method is rapid and readily applicable in a clinical setting to paraffin embedded tissues and will greatly improve the diagnosis and clinical management of cardiac amyloidosis.

351 Cardiac Overexpression of CXCL10 Causes Spontaneous Leukocyte Infiltration but Not Cardiac Dysfunction

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Background: The essential role of chemokines in dilated cardiomyopathy (DCM) has been demonstrated by recent studies. We previously showed the upregulation of cystein-x-cystein (CXC) chemokine ligand 10 (CXCL10) in Coxsackievirus B3 (CVB3)-induced myocarditis, a major cause of DCM.
Design: To explore the contribution of CXCL10 to CVB3-induced myocarditis and associated DCM, we performed functional analyses using newly generated transgenic mice (Tg) that cardiac-specifically overexpress CXCL10.
Results: A transgenic mouse model with cardiac-specific overexpression of CXCL10 was generated. The cardiac specific upregulation of CXCL10 was confirmed by PCR, RT-PCR, *in situ* hybridization, and Western blot analyses. Cardiac-specific expression of CXCL10 resulted in spontaneous infiltration of $CD4^+$ T cell, $CD8^+$ T cell, and NK cell in perivascular and interstitial regions of the myocardium as compared to control wild type littermates by both real time qRT-PCR and immunohistochemical staining. The number of infiltrations was age-dependent, with the greatest number in older Tg mice, but barely any in four-week-old mice. Further, the expression levels of IFN-γ, and counterinflammatory IL-10 cytokine in Tg hearts were significantly elevated as compared to that in wild type mouse hearts, but the expression levels of the pro-inflammatory cytokines (TNF-α, IL-4, IL-5, IL-6, IL-12) were unchanged. Despite the presence of mononuclear cell infiltrations and limited mRNA upregulation of IFN-γ and IL-10 in the myocardium, there were no discernible pathological alterations in the hearts of Tg mice, as revealed by (i) cardiac troponin I levels, a serum marker of myocyte injury; (ii) echocardiography, a measure of heart ejection fraction; and (iii) heart mass/body weight.
Conclusions: These findings indicate that CXCL10 primarily directs T cells and NK cells to the myocardium, and is associated with minor defense immunity but is insufficient to cause cardiac dysfunction.

Cytopathology

352 Cytopathological Changes of Cervical Smears in Patients with Uterine Prolapse: A Major Pitfall for Sqaumous Intraepithelial Neoplasia (Cervical Dysplasia)

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Background: Pitfall of cervical cytology is of utmost importance to be recognized due to its medicolegal consequences. Cytology of cervical smears from uterine prolapse patients can cause changes that may mimic dysplasia changes. Pathologists are likely to mistake these cases if encountered for the first time as dysplasia changes with Human papilloma virus (HPV)- like changes.
Design: Twenty cases of cervical swab from patients with uterine prolapse were studied. All patients had consequent simple hysterectomy due to prolapse symptoms. The patients' age ranged from 35-72 years of age with parity ranged from 4-14 kids.
Results: Cervicovaginal smears showed changes that are seen in cervical dysplasia: increased nuclear cytoplasmic ratio, nuclear membrane irregularities and perinuclear halos in 20/20 cases; discohesiveness of cells in 15/20 cases, cell hugging in 14/20 cases; nuclear hyperchromasia in 11/20 cases.