between these two groups (p=0.2136). The mean ages were 57.43 for node negative tumors and 55.50 for node positive tumors (p=0.2181). There was a significant difference of tumor size between node negative (2.27cm) and node positive tumors (3.55cm), with a p-value less than 0.0001. While we did not observed a significant different for histologic grade between these two groups (p=0.4018); there was a significant difference for nuclear grade between these two groups (p=0.018). There was also difference in HER2 over-expression between these two groups (p=0.0595), but no difference was observed in the expression of ER (p=0.4379) and PR (p=0.6648) between these two groups of tumors.

Conclusions: Tumor size, nuclear grade, and HER2 positivity predict lymph node metastasis in breast carcinomas that have lymphovascular invasion. Tumor type, patient age, histologic grade, and expression of ER and PR are not predictive.

348 Fibroepithelial Lesion with Cellular Stroma: Topoisomerase 2 Is a Helpful Marker To Differentiate Fibroadenoma from Phyllodes Tumor on Needle Core Biopsy

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Background: The differential diagnosis of fibroepithelial lesions with cellular stroma (FELCS) in core needle biopsy (CNB) specimens ranges from fibroadenoma (FA) to phyllodes tumor (PT). The management of these two lesions is different. We intended to explore possible morphologic and immunohistochemical (IHC) parameters that may predict the final diagnosis on the excisional biopsy.

Design: A series of FELCS cases diagnosed on CNB with matching excisional biopsy were retrieved from our files between 2003 and 2009. The following histologic parameters were recorded: stromal cellularity (1, 2, or 3), stromal cell atypia (1, 2, or 3), stromal cell mitosis per ten high power fields, stroma overgrowth, infiltrative edge, stromal cellularity enhanced at epithelium and leaf-like pattern. Patients' age and tumor size were also recorded. The following IHC stains were performed on CNB: KI-67 (clone MIB-1), p53 (clone DO7) and Topoisomerase 2 (TOPO2) (clone EP1054Y). Percentage of positive cells was recorded. Fisher's exact test and Wilcoxon non-parametric test were used for statistical analyses.

Results: The table below illustrates all the findings.

Histologic, Clinical and IHC Finding

	FA (n=8)	PT (n=12)	p value
Age (y), median (range)	42 (35-48)	47 (30-82)	NS
Size (cm), median (range)	1.35 (0.5-2.5)	3.45 (0.5-15)	0.022
Stromal cellularity			
1 or 2	7 (87.5)*	8 (66.7)	NS
3	1 (12.5)	4 (33.3)	NS
Stromal cell atypia			
1	6 (75.0)	5 (41.7)	NS
2 or 3	2 (25.0)	7 (58.3)	NS
Stromal cell mitosis			
No	6 (75.0)	8 (66.7)	NS
Yes	2 (25.0)	4 (33.3)	NS
Stromal overgrowth			
No	5 (62.5)	6 (50.0)	NS
Yes	3 (37.5)	6 (50.0)	NS
Infiltrative edge**			
No	8 (100.0)	6 (66.7)	NS
Yes	0 (0.0)	3 (33.3)	NS
Stromal cellularity enhanced at epithelium			
No	8 (100.0)	11 (91.7)	NS
Yes	0 (0.0)	1 (8.3)	NS
Leaf-like pattern			
No	6 (75.0)	5 (41.7)	NS
Yes	2 (25.0)	7 (58.3)	NS
Median (range) Ki-67 (%)	5 (0-20)	10 (1-50)	NS
Median (range) p53 (%)	2.5 (0-90)	20 (0-80)	NS
Median (range) TOPO2 (%)	0 (0-2)	2 (0-10)	0.037

* No. (%), ** n=9 for PT

Conclusions: Larger clinically measured tumor size and presence of Topoisomerase 2 staining can predict PT on CNB.

349 Breast Hormonal Receptors Test Should Be Repeated on Excisional Biopsies after Negative Core Biopsy

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Background: Accurate estrogen receptor (ER) and progesterone receptor (PR) results are important for therapeutic decision making for patients with breast carcinoma. The purpose of this study was to assess the concordance of breast cancer immunohistochemical receptor assays on core biopsy and surgical specimens.

Design: We identified 176 patients whose core biopsy was performed either at Roswell Park Cancer Institute (RPCI) or at an outside facility between 2007 and 2009. Surgical specimens were processed in RPCI. ER and PR, for biopsies and excisions, were scored using Allred scoring system. While biopsies were processed in 12 different laboratories, stained in 5 different laboratories using 3 different vendors, the excisional biopsies were processed and stained in RPCI using one vendor (Dako). While the following antibodies were used for ER, 1D5, 6F11 and SP1, the following antibodies were used for PR, PgR636, 16 and 1E2 from Dako, Leica and Ventana respectively. Correlation of scores of biopsies with matching excision was analyzed using Spearman correlation coefficient test.

Results: Seventeen (9.7%) patients were biopsied in RPCI and 159 (90.3%) patients in an outside facility. While there were 141 (80.1%) cases positive for ER and 118 (67%) cases positive for PR for the core biopsy, there were 143 (81.3%) cases positive for ER and 130 (73.9%) cases positive for PR for the excision. Concordance for ER and PR was seen in 93% and 89.8% respectively. Table illustrates the concordance between biopsy and excision for both markers based on vendors. Spearman correlation coefficient between biopsy and excision was 0.75 for ER and 0.79 for PR (p<0.0001 each).

Table: Comparison of ER and PR between biopsy and excision based on Vendors.

	Dako (No. 23)	Leica (No. 124)	Ventana (No. 29)	P value
ER: BX+EX+	16 (69.6)*	100 (81.3)	20 (66.7)	0.11
ER: BX+EX-	0 (0)	3 (2.4)	2 (6.7)	
ER: BX-EX+	3 (13)	3 (2.4)	1 (3.3)	
ER: BX-EX+	4 (17.4)	17 (13.8)	7 (23.3)	
PR: BX+EX+	13 (56.5)	85 (69.1)	17 (56.7)	0.48
PR: BX+EX-	0 (0)	2 (1.6)	1 (3.3)	
PR: BX-EX+	2 (8.7)	11 (8.9)	2 (6.7)	
PR: BX-EX+	8 (34.8)	25 (20.3)	10 (33.3)	

* Number (percentage); BX, biopsy; EX, excision

Conclusions: Although there was no uniformity in biopsies processing or staining, practically speaking, ER and PR should be repeated on the excisional biopsies for patients whose core biopsies have negative hormonal receptor.

350 Tissue Factor Expression in Triple-Negative Breast Carcinomas

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Background: Tissue factor (TF) is expressed in a variety of tumor cells and has been linked to cellular signaling, angiogenesis, and tumor progression. However, its role in human cancer is not fully known. Recently, upregulation of TF has been linked to expression of epidermal growth factor receptor (EGFR), a prognostic factor of breast cancer. Triple-negative (ER, PR and HER-2) breast carcinomas (TNBC) belong to a subgroup of breast cancer with aggressive clinical behavior and poor prognosis.

Design: Forty-five cases of TNBC diagnosed from 2003 to 2008 were retrieved from the archive of the Department of Pathology of Temple University. Adequate tissue was available in 41 cases that formed the basis of this study. All patients were female with an age range from 32 to 81. Immunohistochemistry for CK5/6, EGFR and TF was performed, and results were scored as positive (tumor cells stained) or negative (no tumor cell stained). Basal-like carcinoma (BLC) was defined as a TNBC positive for CK5/6 and/or EGFR.

Results: 20 (49%) of patients presented with regional lymph node metastasis, 9 (22%) demonstrated distal metastasis and 24 (59%) had advanced clinical stage (III/IV). All cases were invasive ductal carcinoma (IDC), except for one adenoid cystic carcinoma. 36 of the 40 IDC were histologically high grade and the remaining 4 were intermediate grade. BLC was identified in 36 of the 41 (88%) cases, among which 21 (58%) were positive for both CK5/6 and EGFR, 14 (39%) were positive for only CK5/6 and 1 (3%) was positive only for EGFR. The remaining 5 cases were negative for both markers (non basal-like carcinoma, NBLC). Overall, TF expression was found in 35 of the 41 (85%) cases. TF expression was detected in 31 of 36 (86%) BLC and in 4 of 5 (80%) NBLC. With respect to EGFR expression, 18 of the 22 (81%) cases positive for EGFR expressed TF, however TF expression was also found in 4 of 6 (80%) cases that lacked EGFR expression.

Conclusions: TF expression was found in the majority of cases of TNBC (88%), suggestive that TF expression is linked with the aggressive tumor behavior and poor prognosis of the patients with TNBC. Tumor TF expression was similar in BC (86%) and NBC (80%). However, a close association between TF and EGFR expression was not observed. Further study is warranted to explore the clinical significance of TF expression and its association with EGFR expression in this breast cancer subtype.

Cardiovascular

351 Causes-Mechanisms of Death Following Stage I Repair for Hypoplastic Left Heart Syndrome (HLHS)

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Background: Staged hybrid repair is a recent advancement in treatment of HLHS. Stage I (of 3 stages) includes balloon atrial septostomy and ductus arteriosus stenting (by catheterization) as well as surgical pulmonary artery banding. The causes-mechanisms of death between the stage I and II procedures have not been well-documented at autopsy.

Design: Autopsy reports and microscopic slides were reviewed from 13 consecutive patients (August 2002 - August 2009) who died after first stage repair for HLHS (6 males and 7 females). Causes-mechanisms of death as well as nonfatal complications were recorded.

Results: The mean age at death was 60 days (range 9 to 180 days). Six deaths occurred at < 30 days following stage I repair (group 1) and 7 deaths occurred at > 30 days (group 2). Eleven patients had the complete stage I repair, one had only atrial septostomy and one had only ductus arteriosus stenting. Autopsy permit included no restrictions (n=7), chest and abdomen only (n=2) or chest only (n=4). The causes-mechanisms of death in group 1 were ductus arteriosus closure (n=1, patient had only atrial septostomy), left atrial appendage tear (n=1, occurred during atrial septostomy), arrhythmias that developed during the procedure (n=3) and pneumonia (n=1). Two of the patients with arrhythmias had a myocardial substrate that may have predisposed to arrhythmia (fibrosis and myocyte disarray). The causes-mechanisms of death in group 2 were intestinal necrosis (n=1), myocardial necrosis due to insufficient retrograde flow into the aortic arch (n=1), pneumonia (n=2), pulmonary emboli (n=1), pulmonary vein stenosis (n=1) and sudden death without documented arrhythmia (n=1). Aorta and/or vena cava thrombosis or a significant thromboembolic event were found in four group 2 patients.

Conclusions: Intraprocedural events (arrhythmia, left atrial tear) accounted for 67% of deaths in group 1 patients. Pneumonia and ischemic necrosis (heart, intestines) accounted for the majority of deaths (57%) in group 2. Thrombotic / thromboembolic

events found in 57% of group 2 patients were not observed in group 1. Autopsy results demonstrated differences in causes-mechanisms of death and rates of thrombotic / thromboembolic events in patients who died at < 30 days and > 30 days following stage I repair for HLHS.

352 Usefulness of PCR for *Trypanosoma cruzi* DNA in Endomyocardial Biopsies for Early Detection of Chagas' Disease Reactivation after Heart Transplantation

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Background: Chagas' disease is caused by the protozoan *Trypanosoma cruzi*. Around 20% of infected people develop a chronic, inflammatory cardiomyopathy which may progress to end-stage heart failure. After heart transplantation, Chagas' disease reactivation in the allograft (CDR) is characterized by inflammatory cell infiltration and presence of *T. cruzi* parasites in the myocardium. CDR must be distinguished from acute cellular rejection in endomyocardial biopsies (EMB); for this purpose, we routinely search for parasites in serial HE-stained sections and perform immunohistochemistry for *T. cruzi* antigens (IHC). In this study, we investigated the usefulness of PCR for *T. cruzi* DNA in EMB for the early detection of CDR.

Design: CDR was diagnosed in 6 heart-transplanted, chagasic patients (*T. cruzi* parasites detected in HE-stained sections in 5 EMB and positive IHC in 1 EMB). We examined retrospectively 18 EMB from those patients, collected up to 6 months before the diagnosis of CDR (pre-CDR group) and 15 EMB from 6 additional heart-transplanted, chagasic patients that had never presented clinical or pathological evidence of CDR (control group). Serial sections of the paraffin-embedded EMB were submitted to a PCR-based assay for *T. cruzi* DNA. We used two sets of primers: TCZI/II that amplifies a 188-bp repetitive nuclear sequence of *T. cruzi* DNA and S34/67 that amplifies a 122-bp sequence localized within the minirepeat of the parasite's kinetoplast minicircles (kDNA).

Results: The search for parasites in HE-stained sections and IHC resulted negative in all EMB of pre-CDR and control groups. The results of PCR for *T. cruzi* DNA are presented in the table. There was no statistical difference between pre-CDR and control groups, regarding the number of positive patients or the number of positive EMB (Fischer's exact test).

Number of positive patients or positive EMB in pre-CDR and control groups

Amplified DNA	Pts of pre-CDR group (n = 6)	EMB of pre-CDR group (n = 18)	Pts of control group (n = 6)	EMB of control group (n = 15)
Nuclear	1/6 (16.7%)	2/18 (11.1%)	0/6 (0%)	0/15 (0%)
kDNA	3/6 (50%)	6/18 (33.3%)	2/6 (33.3%)	4/15 (26.7%)

Pts: patients; EMB: endomyocardial biopsies

Conclusions: Amplification of nuclear sequences in a PCR-based assay for *T. cruzi* DNA in EMB may be an early marker of CDR, but amplification of kDNA is unspecific occurring in patients with no clinical evidence of CDR.

353 Detection of C4D and C3D in Endomyocardial Biopsies at and Prior to Diagnosis of Antibody-Mediated Rejection

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Background: C4d & C3d deposition in capillaries of cardiac allografts is associated with antibody-mediated rejection (AMR) & poor graft outcome. Both C4d & C3d immunostaining in endomyocardial biopsies (EMBs) at & prior to diagnosis of AMR have not been examined.

Design: EMBs from 7/97 to 9/05 of patients (pts) with AMR (diagnosed by histological findings & presence of intravascular CD68+ macrophages) & the immediate prior EMB without AMR were compared to EMBs from age- & sex-matched control group who never had AMR. All EMBs were stained with C4d & C3d via immunoperoxidase technique on paraffin-embedded sections. Fishers exact test was used for statistical analysis.

Results: The study group consisted of 89 pts (54 males & 35 females) with a mean age of 43.6 ± 21.1 years. Median time to first AMR biopsy was 197 days post transplant (DPT) (IQR = 1043 DPT). Median time to pre-AMR biopsy was 169 DPT (IQR = 791 DPT). The median pre-AMR to AMR interval was 31 DPT (IQR = 105 DPT). The control group consisted of 90 pts (55 males & 35 females) with mean age of 44.9 ± 20.7 years. Median time to EMB was 171 DPT (IQR = 10.8 DPT).

Table 1: C4d & C3d Staining Patterns for Control, Pre-AMR, & AMR Groups

Group	C4d Staining		C3d Staining	
Group	Negative (0+/1+)	Positive (2+/3+)	Negative (0+/1+)	Positive (2+/3+)
Control	88 (97.8%)	2 (2.2%)	86 (100%)	0 (0%)
Pre-AMR	66 (78.6%)	18 (21.4%)	74 (89.2%)	9 (10.8%)
AMR	56 (64.4%)	31 (35.6%)	72 (82.8%)	15 (17.2%)

Joint C4d/C3d Staining Patterns for Control, Pre-AMR, and AMR Groups

Group	C4d+/C3d+	C4d+/C3d-	C4d-/C3d+	C4d-/C3d-
Control	0 (0%)	2 (2.3%)	0 (0%)	84 (97.7%)
Pre-AMR	9 (10.8%)	9 (10.8%)	0 (0%)	65 (78.3%)
AMR	15 (17.2%)	16 (18.4%)	0 (0%)	56 (64.4%)

As compared to the control group, there were more C4d+ & C3d+ EMBs in the pre-AMR (p-values <0.0001 & 0.0013, respectively) & AMR groups (both p-values <0.0001). There were more C4d+ & C3d+ EMBs in the AMR than pre-AMR group. Respectively, C4d & C3d stayed positive in the subsequent AMR EMB in 94.1% & 75% of pre-AMR EMBs. Moreover, C4d & C3d were positive at time of AMR EMB in 46.7% & 60%, respectively.

Conclusions: C4d & C3d positivity are seen more commonly in EMBs with AMR or before AMR. Since only 35.6% & 17.2% of pts diagnosed with AMR demonstrate C4d & C3d positivity, respectively, additional markers of AMR are needed. C4d & C3d staining will be correlated with clinical, hemodynamic, & antibody data.

354 Decreased Acute Cellular Rejection in Transplanted Heart Biopsies

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Background: Acute cellular allograft rejection (ACR) is the primary cause of morbidity and mortality in heart transplant patients. The pathology classification was modified in 2004 to collapse 1A, 1B, and 2 into one grade (1R). We reviewed our experience with old and new grading system to evaluate any difference in ACR over time.

Design: From 2002 to 2009, 210 cardiac transplants were performed in our medical center. The endomyocardial biopsies (EMBs) were performed for routine surveillance and graded according to the Working Formulations from International Society for Heart Transplantation in 1990 and 2004. Primary pathologist was the same for all biopsies. The pathological data were entered in a database. In this study, 390 EMBs from 23 cardiac allograft recipients transplanted before 12/31/2002 were compared with 797 EMBs from 57 patients transplanted between August 2006 and March 2009.

Results: As shown in Table 1, the number of EMBs with no cellular rejection increased from 61% to 73% (p<0.001). The number of EMBs with ACR decreased from 39% to 27%, as follows: grade 1A (21.0% to 18.7%, p=0.341), grade 1B (11.8% to 5.1%, p<0.001), grade 2 (3.6% to 1.9%, P=0.073), 3A (1.5% to 0.75%, p=0.204), and 3B (1.3% to 0.5%, p=0.146). However, the number of Quilty lesions has remained the same (Quilty A: 10.8 vs. 10.3%, p=0.799) or increased (Quilty B: 6.9% to 12.5%, p=0.003).

Table 1. Comparison of EMB data

Degree of ACR/Quilty	# of EMBs (2002)	percentage	# of EMBs (2006-2009)	percentage	P value
G0	237	60.8	582	73.0	0.000
G1A	82	21.0	149	18.7	0.341
G1B	46	11.8	41	5.1	0.000
G2	14	3.6	15	1.9	0.073
G3A	6	1.5	6	0.8	0.204
G3B	5	1.3	4	0.5	0.146
G4	0	0	0	0	N/A
Total	390	100	797	100	N/A
QA	42	10.8	82	10.3	0.799
QB	27	6.9	100	12.5	0.003

Conclusions: The better management of cardiac transplant recipients including improved immunosuppressive agents, better psychosocial screening, and improved preservation of hearts may have reduced the incidence of ACR, primarily in grade 1B. The clinical significance of decreased ACR needs longer clinical follow-up. However, it seems that if only the 2004 grading system was used, such difference in ACR would be attributed to confusion with Quilty lesion rather than finding a true difference in ACR.

355 Epidemiological and Pathological Characteristics of Cardiovascular Tumors: A 10-Year Study

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Background: Primary tumors of the heart and pericardium are rare (about 5%) compared to secondary tumors. Nomenclature for these tumors evolved in the past years distinguishing well differentiated tumors from myofibroblastic and from undifferentiated sarcomas. This study reviewed the center's experience, and evaluated the pathological characteristics, proliferation indices and clinical outcome.

Design: Review of surgeries and databases was performed from 1999 to 2009. H&E slides were reviewed and tumor classification was updated using immunostains when necessary. Variables like age, sex, tumor location, and histology were analyzed using the chi-square and Mann- Whitney tests to detect significant differences among them. The myxomas were grouped into classic and cellular subgroups. Proliferation markers (p53, MIB-1) and BCL-2 were done on cellular myxomas, inflammatory myofibroblastic tumors (IMT), and sarcomas to determine any relation to clinical outcome.

Results: There were 212 cardiovascular tumors with 165(77%) arising from the heart, 2(0.9%) from the great vessels and 45(21%) as metastatic. The incidences were 0.5% for primary tumors and 0.2% for secondary. Most primary tumors were excisions and 2 were autopsies. Myxomas were the most common (62.3%), mostly in females (p<0.002), more in the left atrium (p<0.000), and were seen in all ages. Benign tumors are IMTs (2.8%), rhabdomyomas (1.4%), hemangiomas (0.9%), and others (0.5%). Primary cardiac malignancies were 5(2.4%) myofibroblastic sarcomas, 2(0.9%) leiomyosarcomas, and 1(0.5%) each for angiosarcoma, liposarcoma, and undifferentiated sarcoma. There were 2 pulmonary artery sarcomas. Most metastatic tumors were pericardial (95.6%), mostly in males (p<0.002), and aged 40-59 years (p<0.000). Cellular myxomas had rare reactivity (<1%) for p53 and BCL-2, and 1-5% reactivity for MIB-1. Similar reactivity is seen with IMTs. Sarcomas showed higher reactivity and deaths occurred at >6% reactivity for p53, >60% for BCL-2 and >22% for MIB-1.

Conclusions: Primary cardiovascular tumors were more common than secondary tumors in our center. Myxoma was the most common benign neoplasm in all age groups. Metastatic tumors were more common than primary malignancies. Cellular myxomas and IMTs have similar clinical behavior. Among the primary malignancies, myofibroblastic sarcomas predominate. Prognostic markers that may predict poor outcome regardless of tumor size were p53 at >6% reactivity, MIB-1 at >33%, and BCL-2 at >60%.

356 Role of Plakoglobin Immunohistochemistry in Diagnostic Evaluation of Juvenile Sudden Cardiac Death

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Background: Juvenile sudden cardiac death (SCD) can be due to a variety of acquired and inherited conditions, and is often the first manifestation of a hidden genetic disease. Arrhythmogenic right ventricular cardiomyopathy (ARVC) due to mutations in desmosomal proteins is one of the most frequent causes of SCD. Autopsy diagnosis of

ARVC is based on the findings of myocardial atrophy and fatty/fibro-fatty replacement. However, cases with mild and segmental fibro-fatty replacement still represent a diagnostic grey zone between desmosomal-related ARVC and non-specific myocardial changes. Immunohistochemical (IH) detection of plakoglobin (PKG), a protein of intercalated disks, has been recently proposed as a diagnostic tool for histologic diagnosis of ARVC. We studied the usefulness of this method to rule out ARVC in cases of juvenile SCD with morphologic features suggestive but not conclusive for the disease.
Design: We selected 4 cases with autopsy features suggestive of ARVC in which a clinical family screening, along with a molecular autopsy of the proband had allowed a post-mortem diagnosis of channelopathy (LQTS, n=1; CPVT, n=1; Brugada syndrome, n=2). As positive controls, we used 3 explanted hearts with clinically and genetically proven ARVC. IH was performed on paraffin slides from both ventricles, with antibodies to PKG and N-Cadherin as internal control, using immunoperoxidase with conventional labeled polymer technology, with a 1: 50.000 antibody dilution.
Results: Plakoglobin was intensely expressed at myocyte intercalated disks, both in the right and left ventricles, in all cases of channelopathies with morphologic changes suggestive of ARVC. In contrast, it was markedly reduced or absent in explanted ARVC hearts, confirming the clinical and morphologic findings.
Conclusions: According to our preliminary results, in cases of SCD with ambiguous morphologic features, diffuse positive stain of intercalated disks is useful to rule out the diagnosis of desmosomal-related ARVC. PKG immunohistochemistry can be an additional tool for autopsy diagnosis, that is crucial to guide the genetic screening of SCD, expecially in absence of a significant clinical history or previous instrumental findings.

357 Histopathological Features and Mitochondrial (mt-) DNA Abundance Correlate with Energy Starvation in Congestive Heart Failure (CHF)

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Background: Myocardial energy starvation in CHF suggests that defective mitochondrial oxidative phosphorylation leads to defective cardiac contractility. We hypothesize that decreased mitochondrial abundance in cardiomyocytes causes energy starvation in CHF by decreasing abundance of mitochondrially encoded elements of the electron transport chain and correlates with histopathological features of CHF.
Design: Human cardiac samples were obtained fresh at the time of orthotopic heart transplantation (under IRB approval) at Emory University and Loyola University Medical Center using standard protocols. CHF samples were classified clinically as ischemic (I; n=24), and non-ischemic (NI; n=21). Samples from non-failing (NF; n=12) hearts were obtained as controls. Samples of left ventricle (LV) myocardium were flash-frozen individually and stored (-80°C). DNA was extracted individually using a high-throughput automation DNA extraction. Steady state abundance of mtDNA and nuclear DNA (nDNA) was determined for each LV sample using Real-Time PCR. mtDNA/nDNA ratios were derived. Data were analyzed statistically and expressed as $\log_{10}$ mtDNA/nDNA ratios of LV extracts (CHF vs. NF). Parallel samples were fixed in formalin and evaluated quantitatively for average nuclear area and cytoplasmic area for each sample (repeated 20 times) using Image J Software (NIH).
Results: CHF Patients with I or NI exhibited decreased LV mtDNA compared to those from NF ($p<0.05$ ANOVA). Histopathological data revealed decreased myocyte volume and decreased nuclear volume in samples from CHF hearts ($p<0.01$).
Conclusions: CHF relates inversely to steady-state mtDNA abundance and nuclear volume. Data support the concept that defective mitochondrial biogenesis is critical to CHF and to the morphological changes seen in CHF.

358 Survey of Current Practice Related to Grading of Rejection in Cardiac Transplant Recipients in North America

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Background: The acceptance and implementation of the International Society for Heart and Lung Transplantation's (ISHLT) most recently adopted (2005) nomenclature for diagnosing cardiac allograft rejection is unknown.
Design: We performed an online survey of pathologists at all cardiac transplant centers in the United States and Canada to determine the range of how cardiac transplant rejection is reported. The survey consisted of a series of questions relating to center volume, rejection grading system used, and reasons for using the aforementioned grading system.
Results: Survey responses were obtained from 96 (77%) of 122 centers contacted, representing 82% of the total center volume in the United States and Canada. Among respondents, 87% reported using the ISHLT-2005 grading system, either exclusively or in combination with other grading systems. Overall, 45% of respondents use only the ISHLT-2005 grading system, 40% issue reports containing both the ISHLT-2005 and ISHLT-1990 grading systems, 12% use only the ISHLT-1990 system, and 3% use either the ISHLT-2005 or the ISHLT-1990 system in combination with an institution-specific system (such as the Billingham system or Texas Heart Institute system). Reported reasons for not utilizing the ISHLT-2005 grading system exclusively were related primarily to (1) the preference of the cardiologists and cardiac surgeons at the particular center (74%), and (2) a belief that the ISHLT-2005 grading system is not as informative as the ISHLT-1990 grading system (52%).
Conclusions: There is appreciable variability in the system used for reporting rejection among North American cardiac transplant centers. Understanding the reasons behind this variability will be crucial for the development and implementation of future cardiac allograft rejection grading systems. Interestingly, the reasons most often cited for lack of exclusive utilization of the ISHLT-2005 system were either clinician/surgeon-driven rather than pathologist-driven or were based on assumptions that have not yet been validated.

359 Correlating Microarray Gene Expression Data with Histopathology in Human Heart Allograft Biopsies

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Background: The histopathological criteria for assessing endomyocardial biopsies are empiric and arbitrary lacking external biological validation. Aim was to correlate gene expression with histopathological lesions and diagnosis based on ISHLT criteria in human heart allograft biopsies.
Design: We performed histologic and microarray analysis on 105 endomyocardial biopsies from 45 heart allograft recipients. We included 82 protocol biopsies (PB) and 23 biopsies done for clinical causes (BFC), 70 obtained within the first year after transplantation and 35 taken later. Genome-wide expression data were correlated as pathogenesis-based transcript (PBTs) sets to histological lesions and diagnosis as well as to left ventricular ejection fraction (LVEF). PBTs are a priori defined gene sets reflecting major biological processes in allografts, e.g. T cell infiltration, myocyte dedifferentiation. Groups of related correlations were identified by cluster analysis.
Results: There was strong stereotyping of molecular changes: inflammation (T cell, macrophage, IFNG effects) strongly correlated with increased expression of injury induced genes and decreased expression of genes associated with myocyte function. The changes were greater in BFC and in early biopsies than in PB and late biopsies. Expression of transcripts associated with B cells and immunoglobulins strongly correlated with time post transplant and with presence of Quilty type B lesions. LVEF was lower in biopsies with higher molecular disturbances, including transcripts associated with myocyte injury. Histological lesions most correlated with high PBT scores were interstitial edema, hemorrhage, and capillaritis. The current histologic criteria for acute cellular rejection, i.e. interstitial infiltrates and myocytolysis – showed no association with the molecular features of the biopsy. The molecular burden of inflammation and loss of myocyte function associated transcripts was most closely correlated with Quilty type B lesions but not with other ISHLT diagnosis.
Conclusions: We conclude that measurement of transcriptome abnormalities reflects a stereotyped disturbance in the endomyocardium with an increase in inflammation/injury and decrease in myocytal transcripts, that translates into impaired function and pathologic lesions, but not current ISHLT categories for rejection.

360 Epstein-Barr Virus-Associated Diffuse Large B-Cell Lymphoma (DLBCL) Arising on Cardiac Prostheses

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Background: Primary cardiac lymphoma is extremely rare and lymphoma arising in association with prosthetic valves has been described in only 3 single case reports. We describe three patients with diffuse large B-cell lymphoma (DLBCL) involving prosthetic heart valves and a synthetic tube graft.
Design: Patients with primary DLBCL involving prosthetic heart valves or synthetic grafts either treated at our institution or reviewed as a pathology consultation case were identified through a laboratory information system database query. Medical records were reviewed to systematically abstract patient demographics, presenting signs and symptoms, intraoperative findings, prosthetic valve or graft characteristics, postoperative lymphoma staging, and patient outcomes. Histologic slides were reviewed and immunohistochemistry was performed for all cases using formalin-fixed paraffin-embedded sections, including stains for: CD3, CD10, CD20, BCL-2, BCL-6, MUM1, and HHV-8. In-situ hybridization for EBV EBER mRNA was also performed on paraffin sections.
Results: Three patients were identified with DLBCL involving a bioprosthetic aortic valve, a mechanical aortic valve, and a composite ascending aortic graft. All specimens showed shallow layering of acellular fibrinous debris over the prosthetic or synthetic materials, with neoplastic lymphocytes present at the luminal surface. There were frequent mitoses and abundant karyorrhectic debris. All demonstrated a non-germinal center B-cell phenotype. All three cases were positive for Epstein-Barr virus, but there was no staining for HHV8. There was no other evidence of distant disease at the time of diagnosis and no recurrence or dissemination occurred after surgical removal of the prosthesis, though follow-up was limited.
Conclusions: Based on 2008 WHO diagnostic criteria, we believe these cases should be classified as DLBCL associated with chronic inflammation (DLBCL-CI). However, unlike the characteristically poor prognosis reported in this entity, we hypothesize that the disease resectability in these cardiac sites, in many cases, may allow for a better prognosis than DLBCL-CI at other less resectable sites.

361 Additional Prognostic Contribution of C3d Staining in Antibody Mediated Rejection of Cardiac Allografts

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Background: Antibody mediated rejection (AMR) of cardiac allografts is a complex immunologic process initiated by antibodies directed against antigens expressed on donor endothelium. Ensuing events lead to the pathologic hallmarks of AMR in the acute phase (complement activation and macrophage accumulation). Staining for complement component C4d is the mainstay for detecting complement activation in endomyocardial biopsies because it persists in tissues by covalent binding. Staining for C3d ("downstream" from C4 in the complement cascade) is routinely performed at some institutions in combination with C4d, but there are few studies addressing the additive diagnostic and prognostic value of C3d deposition.
Design: The patient population was comprised of allograft recipients tracked in the Utah Transplant Affiliated Hospitals (UTAH) cardiac transplant database (28,450 biopsies on 986 patients). Results of immunofluorescence staining for C3d (AbD Serotec clone

053A-514.3.1.4) and C4d (AbD Serotec clone 10-11) were scored on a 0, 0.5+ (trace), 1+, 2+, 3+ scale, and all data from the biopsies were prospectively recorded at the time of biopsy sign out. Scores of 1+ or greater were considered positive. A Cox proportional hazard model using the endpoint of cardiovascular mortality (CVM) was utilized to evaluate combinations of C3d and C4d staining.

Results: 3735 biopsies from 422 patients in the database had sufficient information to be included in the analysis. The data are summarized in the table below.

Cox Hazaard Model for C3d and C4d Staining

	n=	% CV mortality	HR
C4d+ C3d+	208	0.5	2.47
C4d+ C3d-	229	2.6	12.0
C4d- C3d+	211	0.9	6.65
C4d- C3d-	3070	0.3	1.0

CV: cardiovascular; HR: hazard ratio

Most biopsies (82%) were negative for both C4d and C3d and patients with this staining pattern had the lowest CVM. Compared to cases with C4d staining alone, those with both C4d and C3d deposition paradoxically had superior outcomes (hazard ratio = 0.18 among all C4d positive cases).

Conclusions: Detection of C3d in transplant endomyocardial biopsies is associated with a small but significant difference in cardiovascular mortality, adding clinically useful information to staining for C4d alone. Mediation by complement pathway regulators, indicated by the disparate staining patterns, may account for this difference, but further study is needed.

362 New Insights into Stentless Porcine Bioprosthesis Failure

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Background: The Medtronic Freestyle valve is a stentless porcine valve fixed in glutaraldehyde at "zero" pressure on the cusps and treated with a-amino oleic acid. This valve reportedly has excellent clinical and hemodynamic results, but has had some failures, however little has been reported about its long-term pathology.

Design: Seventeen Freestyle valves (explanted 2003 to2009) were reviewed to assess reasons for bioprosthesis failure. Clinical data, including implant age, gender, native aortic valve lesion and implant duration were recorded. All valves were examined in detail, using histochemistry and immunohistochemistry to identify morphological changes and cellular and humoral responses.

Results: One Freestyle valve, explanted for mitral valve endocarditis on the fifth postoperative day, was excluded from analysis. The average implant duration was 71±35.2 months (6±2.9 years). Six valves were explanted for infective endocarditis, six for aortic insufficiency, and four for aortic stenosis. Infective endocarditis was seen in six, calcification in eleven, pannus in fifteen, twelve showed thrombus, cusp tears in nine and 10 showed old needle tract like injuries in the porcine aorta. Acute inflammation was seen in one and a chronic inflammatory reaction involving the xenograft arterial wall was seen in fifteen of sixteen valves. The cells were comprised of macrophages and lymphocytes. The lymphocytes were T cells(CD8 positive) and B cells. Significant damage to the porcine aortic wall was seen in fifteen cases and cusp myocardial shelf damage in seven cases. All cases stained positively for IgG and C4d par.

Conclusions: The porcine aortic cusps showed no significant cellular reaction. The porcine aortic tissue showed multifocal T cell mediated rejection associated with significant porcine aortic medial damage, consistent with dilatation of the porcine aortic root. This likely lead to porcine valular incompetence. The demonstration of IgG and C4d staining suggests the likelihood of humoral rejection, in addition to the cellular. One possibility underlying this is, that the porcine aortic tissues are inadequately fixed and hence the retained antigenicity. This is one of the few demonstrations of a rejection reaction to porcine bioprosthetic tissues, associated with bioprosthesis failure, and needs further studies.

363 Sub-Analysis of Obesity in Autopsy Series of Maternal Cardiopulmonary Deaths in Two Tertiary Centres in the United Kingdom

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Background: Obesity in pregnancy has become a significant maternal risk. The aim of this study was to investigate obesity in maternal cardiopulmonary deaths in two tertiary centres in the UK.

Design: In our retrospective study of 81 maternal cardiopulmonary deaths collected from our combined archives of autopsies and consultation cases from 1994 to 2009, we analysed 47 cases (58%) where body mass index (BMI) data was available.

Results: In 47 cases of maternal deaths with known BMI, thirty (64%) were found to be obese (BMI ≥30) or overweight (BMI ≥25, <30). Obesity (n=20) including six morbidly obese (BMI ≥40) predominated over overweight cases (n=10). The proportion of obese/overweight (BMI ≥25) increased progressively by 17% in the period of 1998 to 2009. The predominant cardiac causes of death in the BMI ≥25 group were sudden cardiac death with morphological normal heart followed by cardiomyopathy mainly left ventricular hypertrophy (LVH) (Table 1). Simple regression analysis revealed the strong correlation between heart weight and BMI in subjects with normal heart and LVH ($r = 0.81$, $P < 0.001$). Obesity was also linked to pulmonary embolic disease and pulmonary hypertension.

Table 1. Causes of maternal death according to BMI

	BMI<25 (n=17)	BMI≥25 (n=30)	Total (n=47)
Sudden death with morphologically normal heart	3	7	10
Cardiomyopathy	4	4	8
CA pathology	3	1	4
Other cardiovascular disease	2	5	7
Pulmonary embolic disease (inc. AFE)	2	7	9
Pulmonary hypertension	1	4	5
Thrombotic disease	2	2	4

CA; Coronary artery, AFE; Amniotic fluid embolism

Conclusions: Our study highlights the link between obesity and maternal cardiopulmonary death.

364 Predictive Value of the Extent of Fibrosis on the Progression of Dilated Cardiomyopathy

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Background: Dilated cardiomyopathy is a primary myocardial disease characterized by dilatation and impaired ventricular contraction. It has no typical histopathologic features although fibrosis, ranging from mild to extensive is a constant feature. It is unknown whether extensive fibrosis predicts a worst prognosis in patients with dilated cardiomyopathy. The objective of this project is to compare the progression of disease in patients with the highest degree of myocardial fibrosis with those with the lowest extent of fibrosis.

Design: Thirty consecutive adult patients that underwent allograft cardiac transplantation between 2004 and 2008 at the University of Alabama at Birmingham for idiopathic dilated cardiomyopathy were included. Morphometry to quantify fibrosis was performed on picrosirius red stained slides (5 per patient) of ventricular muscle. The total fibrosis of the five sections was expressed as percentage of the myocardial mass. The 15 patients with the highest percentage of fibrosis were contrasted with the 15 patients with the lowest extent of fibrosis in terms of demographics, duration of the heart failure from beginning of symptoms until transplantation, association with diabetes and renal failure, severe mitral regurgitation and need for defibrillator placement.

Results: Patients in the upper half degree of fibrosis (17.7 ±3.9%) had statistical non significant differences with the lower half (9.6% ± 3.5%) with regards to age at transplantation (44.1 ±10.6 vs 50.7±12.9 years), gender (10 males vs 9 males) or race (7/15 whites vs 9/15 whites). Patients in the higher fibrosis group had a longer time course between beginning of symptoms and transplantation (8.9± 5.6 vs 6.2± 6.4 years). Moreover, 13/15 patients in the higher fibrosis group had a heart failure history longer than 5 years while only 7 out of 15 in the lower fibrosis group. Patients in the higher fibrosis group had more prevalence of diabetes (5/15 vs 1/15), and a trend toward less mitral regurgitation (8/15 vs 10/15). 13/15 patients in both groups had a cardioverter-defibrillator implanted.

Conclusions: The main finding is that the highest degree of fibrosis was associated with a longer disease course, suggesting that fibrosis is not associated with a faster course of heart failure. Cardioverter defibrillators were as likely to be implanted in either group. Patients with diabetes were more prevalent in the higher fibrosis group but mitral regurgitation in the lower group, in keeping with the known extracellular matrix degradation in mitral regurgitation.

365 Incidence of Focal Myocarditis at Autopsy

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Background: The significance of focal cardiac inflammation in sudden death is often unclear. There are few studies addressing the incidence of presumed incidental focal infiltrates at autopsy.

Design: We prospectively assessed inflammation in 393 consecutive hearts seen in consultation from 2 medical examiners' offices. Hearts were received intact and sectioned uniformly in 5 areas (3 left ventricle, one ventricular septum, and one right ventricle) and reviewed histologically by a single pathologist. Inflammation was classified as focal, multifocal, inflammation with necrosis, and eosinophilic. Histologic findings were retrospectively correlated with other cardiac findings, history of drug and medication use, post-mortem toxicology, and cause of death in the final autopsy report. 9 cases with myocarditis as a primary cause of death were excluded. Of the 384 hearts, there were 239 cardiac non-inflammatory deaths. There were 51 natural non-cardiac deaths, and 94 unnatural deaths.

Results: In the 384 hearts, any infiltrates were found in 18%, multifocal infiltrates in 9%, inflammation with necrosis in 2%, and eosinophilic myocarditis in 4% of hearts. Incidental infiltrates were most frequent in natural non-cardiac deaths (31%), followed by drug-related deaths (20%), natural cardiac deaths (16%), and traumatic deaths (12%). Infiltrates with necrosis were present in 4% of arrhythmic deaths with no other cause, in 3% of cardiac deaths with cardiomegaly, in 2% of natural non-cardiac deaths, in 1 traumatic death (3%), in 1 coronary death (1%), and in 0 other cardiac or drug-related death. Any infiltrate was most frequently seen in patients on antibiotics (55%) or neuroleptic drugs (30%), and eosinophilic infiltrates presumed secondary to hypersensitivity were seen in 18% of patients on antibiotics and 5% of patients on other medications. Contraction band necrosis was most frequent in resuscitation or brain death > 3 hours (55%) and prolonged resuscitation < 3 hours (12%) vs. 2% of non-resuscitated deaths.

Conclusions: Incidental cardiac inflammatory infiltrates without necrosis are not uncommon, but focal myocarditis, as defined as inflammation with necrosis, occurs in <5% of hearts, and should be considered a possible contributory factor.

366 Variation in Both Macroscopic and Microscopic Features of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare dominantly inherited cardiac disease characterised by ventricular arrhythmias and sudden cardiac death (SCD).

Design: We retrospectively identified 73 referrals of sudden cardiac death with ARVC.

Results: The majority of cases in this study were male (n=54) with a median age of 35 years. Nine cases had a family history of cardiac disease and 4 had received a clinical diagnosis of ARVC during life. SCD occurred during exertion (n=27), at home (n=22), community (n=13), hospital (n=4) and unknown (n=9). Where an opinion was provided by the referring pathologist (n=48) the macroscopic findings were classic ARVC (n=19), hypertrophy (n=10, LVH: 9, BVH: 1), LV fibrosis (n=6), normal (n=6), dilated cardiomyopathy (n=5) and ischaemic heart disease (n=2). Of the 43 hearts we analysed, our macroscopic findings were of classic ARVC (n=22), hypertrophy (n=12, LVH and RV fat: 6, LVH: 3, right ventricular hypertrophy: 2, BVH: 1), LV fibrosis (n=5) and normal (n=4). Histologically our analysis identified the predominance of biventricular involvement (n=50), exclusive right ventricular involvement (n=18), and a smaller group with exclusive left ventricular involvement (n=5). ARVC is difficult to diagnose and is prone to misdiagnosis when relying on macroscopic findings alone, which can be variable.

Conclusions: Our study shows that even with specialist examination there was a spectrum of macroscopic findings in ARVC that apart from the classic presence of fat included hypertrophy, fibrosis and even no abnormal features. Therefore, a detailed histological analysis is essential to confirm the diagnosis which can often mimic other cardiomyopathies. A correct diagnosis is important for family members as this is a genetically inherited disease.

367 Inflammatory Aortic Aneurysm: Possible Manifestation of IgG4-Related Sclerosing Disease

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Background: Inflammatory aortic aneurysms (IAA) are associated with autoimmune disease; however, the precise pathogenetic mechanism still remains unclear. In this study, we investigate the hypothesis that IgG4-related autoimmune reaction is involved in the formation of IAA, like various other idiopathic sclerosing lesions such as those involving the pancreas and retroperitoneum.

Design: We studied clinico-pathologic features of 23 patients with IAA and 11 cases of atherosclerotic aortic aneurysms (AAA) served as a control group. These cases were retrieved from the surgical pathology files of our hospital from 1995 to 2007. We evaluated the expression of IgG4 in both IAA study and control group. The number of IgG4 positive plasma cells was scored semi quantitatively per single 20X field as follows: 0 (no positive plasma cells), 1(≤20 cells), 2(21 to ≤50 cells), and 3(>50cells).

Results: Of the 23 patients, 20 were males and 3 were females (M: F ratio 6:1); age ranged from 43 to 81 years (average 64.3 years). Clinically, an abdominal mass was detected in 19 patients and abdominal pain was present in 4 patients at presentation**.** Histologically, all 23 cases of IAA formed a mass that displayed inflammatory myofibroblastic tumor-like features. Immunohistochemically, the number of infiltrating IgG4-positive plasma cells in IAA cases exceed that of AAA cases. Score of 0 was seen in 2/23 of IAA and 3/11 of AAA patients; score of 1 was seen in 7/23 of IAA and 5/11 of AAA patients; score of 2 was seen in 1/23 of IAA and 3/11 of AAA and score of 3 was seen in 13/23 of IAA and 0/11 of AAA patients. Thus, 57% of IAA cases showed score 3 of IgG4-positive plasma cells, whereas none of the 11 cases of AAA showed score 3 IgG4-positive plasma cells (P=0.0018, Fischer's exact test).

Conclusions: Our findings suggest that IAA may be an aortic manifestation of the IgG4-related sclerosing disease, and not a simple inflammatory aneurysm. The high number of positive plasma cells, >50 plasma cells/one 20X field is more specific for the IAA than for AAA; however, lesser number can be seen in both IAA and AAA patients.

368 Cardiac Myxomas and Plakophilin-2 Positive Cell-Cell Junctions: A Possible Novel Immunocytochemical Marker

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Background: As the histogenesis and the differential diagnosis of subforms of cardiac myxomas are still controversial subjects, we applied immunocytochemistry using molecular markers for cytoskeletal and junctional proteins, to improve the cell biological basis for myxoma characterization.

Design: We studied 21 cardiac myxomas (10 M, 11F; mean age 56,5±17,13). To examine the mesenchymal differentiation state and the junction proteins antisera against vimentin, desmin, actin, myosin or keratin 8 and 18; N-and E-cadherin, cadherin-11, VE-cadherin, α- and β-catenin, p120, vinculin, α-actinin, afadin, p0071, ARVCF, desmoplakins-1,-2, plakophilin-1,-2,-3, desmocollins1,3 and desmogleins1,2,3 were used.

Results: All myxoma cells were positive for vimentin and also contained smooth muscle α-actin. The tumor cells were connected by adhering junctions (AJs) positive for the *arm*-repeat proteins β-catenin, plakoglobin, protein ARVCF and protein p0071, as well as for α-catenin and afadin. Surprisingly, however, a considerable proportion of the myxoma cells were connected by AJs that in addition also contained plakophilin-2 (PKP2), generally known as an obligatory component of desmosomes of proliferatively active epithelial and carcinoma tissues and cell cultures.

Conclusions: The existence of a subpopulation of PKP2-positive AJs has recently also been noted in certain other soft tissue tumors and mesenchymally derived cells of high proliferative activity. These findings are also important in view of the architectonically organizing role of PKP2 in diverse cell types. These results are discussed in relation to current concepts of origins of cardiac myxomas, the potential value of a differential diagnosis of molecularly defined myxoma subclasses and the molecular functions of PKP2.

369 Mitral Valve Prolapse and Sudden Cardiac Death in the Young

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Background: Mitral valve prolapse (MVP) occurs in up to 5% of the general population. Since the disorder may be associated with sudden death (SD), the aim of our study was to evaluate the prevalence of MVP in young SD victims and the pathological substrate of electrical instability.

Design: The study has been carried by selecting young SD victims with MVP as the sole cardiac abnormality found at autopsy and 15 age-matched controls who died due to extracardiac causes (mean age 28 years, range 15-43). Gross and histology were carried out according to the SD protocol with sampling from the mitral valve leaflets and ventricular myocardium. In selected cases, primary antibodies against the phosphorilated form of Smad 2 were used.

Results: MVP was the cause of SD in 27 (10 M, 17 F, mean age 29,7 years, range 14-40) out of 481 cases of cardiovascular SD (6%). The mean weight of the heart was 415,43±153,5g (p<0,0001). MVP leaflets had a four-fold increase in thickness compared to the normal valves (2,09±0,23, p<0,0001) with fragmented, irregular elastin and collagen and accumulation of proteoglycans. Significant endoperimysial and replacement type fibrosis was observed in patients with MVP, particularly at the level of papillary muscle implantation (100%). By histomorphometry, fibrosis was 26,9±10,9% vs 7,2±4,7% in controls (p<0,0001) and cardiomyocyte diameter was 17,6±4,9 vs 13,2±0,8 in controls (p=0,0006). Immunohistochemistry showed increased nuclear staining for of p-Smad-2 in both mitral valve and cardiac interstitium of MVP cases (p=0.02).

Conclusions: MVP represent a no-so rare cause (6%) of SD in the young due to fatal arrhythmias. The electrical instability seems associated to endoperimysial fibrosis and replacement-type fibrosis, even in the setting of still competent mitral valves, due to a concomitant myocardial involvement ("valvular cardiomyopathy"). These findings suggest a potential role for risk stratification of tissue characterization by late-enhancement cardiac magnetic resonance in MVP patients.

370 Thoracic Lymphoplasmacytic Aortitis Is Often Associated with IgG4-Related Systemic Disease

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Background: We hypothesized that IgG4-related systemic disease accounts for a subset of cases of thoracic aortitis and for a significant fraction lymphoplasmacytic thoracic aortitis cases. To test this hypothesis, we reviewed the experience at our institution with thoracic aortitis over a five-year period. We also sought to establish pathologic criteria for identifying involvement of the thoracic aorta by this disorder.

Design: We searched our Pathology Service database to identify all patients with non-infectious thoracic aortitis who underwent resection over a 5-year time span. The inclusion criterion was the presence of chronic inflammation that was not characteristic of either atherosclerosis or aortic dissection. The exclusion criteria were a history of previous aortic surgery or evidence of an infectious aortitis. We subclassified the non-infectious aortitis cases into two categories based on the nature of the inflammatory component. Those cases with granulomatous inflammation with or without a significant plasma cell component were classified broadly as "granulomatous". Cases with lymphoplasmacytic infiltrates in which granulomatous inflammation was absent were classified as lymphoplasmacytic aortitis. All cases of lymphoplasmacytic aortitis along with representative cases of giant cell aortitis and atherosclerosis were stained by immunohistochemistry for IgG4 and CD138, and the fraction of plasma cells that stained for IgG4 was determined.

Results: Of 638 resected thoracic aortas, 33 (5.2%) contained non-infectious aortitis. Four of these cases (12% of all patients with non-infectious aortitis) had histologic features of lymphoplasmacytic aortitis. Three of those four cases (9% of non-infectious aortitis cases) demonstrated pathologic involvement by IgG4-related systemic disease. Among those three cases, an elevated proportion of plasma cells (0.82±0.08) stained for IgG4, compared with cases of giant cell aortitis (0.18±0.13) and atherosclerosis (0.19±0.08) (P < 0.00001). Follow-up in two of these patients confirmed systemic involvement by IgG4-related systemic disease.

Conclusions: IgG4-related systemic disease accounted for 75% of lymphoplasmacytic aortitis cases and approximately 9% of all cases of non-infectious thoracic aortitis in our institution during a five-year period. Immunohistochemical assessment of the percentage of plasma cells that stain for IgG4 in resected aortas is helpful in identifying patients who have IgG4-related systemic disease.

371 An Autopsy Investigation of Dissections of the Coronary Arteries and Bypass Grafts

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Background: Coronary arterial dissections may be restricted to the coronary arteries or may occur as an extension of aortic dissection. Spontaneous dissections of the coronary arteries are uncommon with two-thirds of patients dying suddenly. In the hospital setting, iatrogenic coronary arterial dissections are well-documented but rare complications of cardiac catheterization, percutaneous coronary intervention (PCI) and cardiac surgery. Dissections of internal mammary artery or saphenous vein grafts are even more rarely documented in the literature. The purpose of this study was to determine the presentation, associations and outcome of dissections of the coronary arteries and bypass grafts.

Design: A search of the autopsy records from 1993 to 2008 for coronary dissections including both native and bypass grafts was performed.
Results: A total of 17 cases of dissections of the coronary arteries and bypass grafts were found. There were 10 women and 7 men with age ranging from 28 to 82 (median age of 62). Dissections of native coronary arteries (11 cases; 8 female:3 male) involved the left coronary arteries in all but 1 patient. Four patients had secondary coronary dissection occurring as an extension of acute ascending aortic dissection while iatrogenic etiology was due to PCI (4) and aortic valve replacement (2). One patient with segmental mediolytic arteriopathy who died of hemoperitoneum was found to have dissection of the left circumflex artery. There were 6 cases (2 female:4 male) of dissections of bypass grafts identified with involvement of the internal mammary artery graft in 4 and saphenous vein graft in 2. Five patients in this latter group underwent coronary artery bypass grafting and one occurred as a complication of aortic valve replacement. Majority of patients (59%) died of myocardial infarction within 1 to 4 days.
Conclusions: Iatrogenic and secondary dissections of native coronary arteries were more common in females and usually involves the left coronary arteries. In contrast, dissections of bypass grafts was observed more frequently in males and were associated with cardiac surgery. Segmental mediolytic arteriopathy is a rare cause of spontaneous coronary dissection.

372 Right Atrial Tumors and Tumor-Like Lesions, a Clinicopathologic Study of 54 Cases

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Background: Cardiac tumors are rare, and those arising in the right atrium form a heterogenous group of tumor and tumor-like conditions that have not yet been studied extensively in a single series.
Design: Fifty-four cases of tumors arising in the right atrium were collected retrospectively from 1995 to 2009 from the files of the Armed Forces Institute of Pathology. The clinicopathological characteristic of benign and malignant proliferations of tumors primarily centered in the right atrium were studied.
Results: Patients range from 6 to 81 years (mean 48.8, SD 18), with 28 males and 26 females. Tumor size ranged from 3 to 20cm. Most common presentation was shortness of breath (18%), followed by chest pain (11%), and other included hemoptysis, pericardial effusion, syncope and arrhythmias. Neurologic symptoms were present only in myxomas (2 cases). Ten cases were incidentally found on imaging or during surgery. There were 31 benign proliferation that included 9 thrombus, 5 fibroinflammatory proliferations (2 of which were associated with clinical and histologic features of sclerosing mediastinitis), 4 cardiac myxomas, 4 lipomatous hypertrophy of the atrial septum, 2 hamartomas of mature myocytes, 2 paragangliomas, 1 nodular tuberculous infiltrate, 1 inflammatory myofibroblastic tumor, 1 cardiac fibroma, 1 hemangioma and 1 leiomyoma. Malignant tumors were 16 primary sarcomas (13 angiosarcomas, 2 synovial sarcomas, 1 pleomorphic sarcoma), 4 lymphomas and 3 metastases (2 melanomas, 1 metastatic adenocarcinoma). Clinical presentation, age, tumor size and sex did not correlate with malignant diagnosis.
Conclusions: Right atrial tumors represent a variety of benign and malignant condition with varied clinical presentation and histologic appearance. Most are benign and include non-neoplastic proliferations. Malignant cases are more homogeneous with angiosarcomas most common, followed by lymphoma and metastases.

373 Immunohistochemical Expression of N-Cadherin, but Not Plakoglobin and Plakophilin, Is Decreased in Pathologically Diagnosed Autopsy-Based Cases of Arrhythmogenic Right Ventricular Cardiomyopathy

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic disorder related to mutations in desmosomal proteins. There have been few histologic studies quantitating expression of desmosomal proteins in autopsy samples of AC.
Design: We studied 29 patients (20 males, 9 females) dying suddenly with ARVC. Their age at death was 33 ± 4 and 32 ± 6 years, respectively. Control subject tissues were 15 men and 7 women, mean ages 36 ± 4 and 32 ± 6 years, respectively. Sections of heart were taken from short axis cuts: 25 sections from control tissues (10 right ventricle-RV, 12 left ventricular free wall-LV, and 3 ventricular septum-VS) and 58 sections from AC (26 RV, 23 LV, and 9 VS). Areas free of fibrofatty change were assessed. Immunohistochemical stains against plakoglobin, plakophilin, and N-cadherin were applied and area expression analyzed by both computerized morphometry correlated with a three-point scale of staining intensity and semi-quantitatevely independently by two pathologists.
Results: The mean area of plakoglobin (5.7%) and plakophilin (5.4%) showed no difference by gender, cardiac site (left ventricle, right ventricle and ventricular septum), patient age, or presence of ARVC. The mean area of N-cadherin staining showed no difference by gender (5.1 ± 0.5% in men vs. 5.1 ± 0.3% in women, p=.99), age (p=.08), or cardiac site (p = 0.7). The mean % staining of N-cadhrein by morphometry was 6.7 ± 0.4% in controls (range 2-14%, vs. 4.5 ± 0.3% in ARVC (ragne 1-14%), p=.0009. A positive predictive value of weak (1+ staining) for ARVC was 76%, with a negative predictive value of 50% (88% sensitivity, and 30% specificity, respectively). By multivariate analysis, % N-cadherin staining was inversely proportional with the presence of ARVC, independent of other variables (p=.0001).
Conclusions: We conclude that immunohistochemical evaluation of plakophilin and plakoglobin does not distinguish ARVC from controls. The relationship between specific mutations in cases of pathologically proven AC and the expression of desmosomal-related proteins needs to be further evaluated. N-cadherin is significantly decreased, but as a qualitative measure is not a specific diagnostic tool.

374 Osseous Metaplasia in Calcific Aortic Valve Stenosis: Role of Congenital Bicuspid Valves

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Background: Calcific aortic valve stenosis (CAVS) is prevalent in aging populations, and is the most common pathology in aortic valves (AVs) requiring surgical excision; the pathogenesis is uncertain and controversial. We correlated the clinical and pathologic characteristics of AVs excised for CAVS that also demonstrate osseous metaplasia (OM).
Design: A retrospective analysis was performed for 2087 native AVs excised for CAVS at Brigham and Women's Hospital from January 2003 to July 2009. Cases of active endocarditis were excluded, as were fragmented valves where cuspal number could not be evaluated; 37 glutaraldehyde-pretreated bioprosthetic AVs excised for calcific degeneration were also examined, implanted from 2-24 years (mean 11.3). Patient demographics were correlated with histologic features (including OM) as diagnosed on paraffin embedded, formalin-fixed, decalcified H&E stained sections.
Results: Among 2087 native AVs with CAVS, 1597 (76%) were tricuspid (TC), 486 (23%) were bicuspid (BC), and 4 (0.2%) were unicuspid, with an overall M:F ratio of roughly 1.5:1. Overall, OM was present in 15% of valves with CAVS. OM was approximately twice as common in BC valves versus TC valves (23.5% vs. 12.6%, Z=5.85), with an earlier mean age of excision (59.7 vs. 75.6 years, p<0.0001). OM was also more common in valves removed from males versus females, in both BC (26.6% vs. 21.7%, Z=2.29), and TC valves (14.3% vs. 10.5%, Z=2.31), with an earlier age of excision (BC: 58.9 vs. 61.6 years, p<0.01; TC: 75.0 vs. 76.3 years, p<0.01). Notably, OM was not observed in any bioprosthetic AVs excised for calcific degeneration.
Conclusions: OM is a common finding in native AVs excised for CAVS, and is more frequent in congenital bicuspid valves. The higher frequency of OM in BC valves with CAVS at an earlier age suggests an inherent susceptibility of these congenitally abnormal valves, possibly attributable to mechanical effects or an intrinsic molecular phenotype of the valve cells. The higher incidence of OM in men further suggests a role for sex hormone modulation of the metaplastic process. The absence of OM in non-viable bioprosthetic AVs suggests osteoblastic transformation of intrinsic cells rather than recruitment of circulating stem cells. These findings can direct future mechanistic studies in unraveling the pathogenesis of CAVS.

375 Ascending Giant Cell Aortitis without Systemic Symptoms Is Associated with an Increased Frequency of Subsequent Distal Aortic Events

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Background: In patients undergoing resection of the ascending aorta for aneurysm or dissection, giant cell aortitis (GCA) is occasionally identified upon pathologic examination. Frequently, ascending GCA is present without systemic systems of vasculitis (GCA-WSS). The clinical significance of GCA-WSS has been unclear. Specifically, it has not been established if patients with ascending GCA-WSS are at increased risk for more distal aortic events on long-term follow-up.
Design: Ascending aortic segments resected for aneurysm or dissection between 1980 and 2004 were reviewed. GCA-WSS was identified by the presence of granulomatous inflammation with or without giant cells. Exclusion criteria included prior or concurrent evidence of systemic rheumatologic disease, age less than 50, mycotic / infectious aortitis, lymphoplasmacytic aortitis, and follow-up of less than fours years duration. Twelve GCA-WSS cases with adequate follow-up were identified. For each GCA-WSS case, 2 non-aortitis control ascending aorta cases were identified. Aortitis cases and controls were matched for age, gender, indication for surgery, date of surgery, type of surgery, and follow-up duration. In both groups, follow-up included imaging with CT and/or MR for the majority of the patients. Aortic events were defined as operations, new aneurysms greater than 5 cm, ruptured aneurysms, or dissections involving the descending thoracic or abdominal aorta.
Results: 5 of the 12 GCA-WSS patients (42%) experienced distal aortic events during follow-up. There were new large thoracoabdominal or descending thoracic aortic aneurysms in three patients, and ruptured thoracoabdominal aneurysms in two additional patients. Three of these 5 patients underwent subsequent aortic surgery. In contrast, only 1 out of 24 patients (4%) in the non-aortitis group had an event, a new thoracoabdominal aneurysm. The difference in the frequency of events is statistically significant, P=0.01.
Conclusions: In long-term follow-up, patients with GCA-WSS are at significantly increased risk for distal aortic events compared with non-aortitis patients. In GCA-WSS patients, subsequent aortic events occur most often in the descending thoracic aorta and/or suprarenal abdominal aorta rather than the infrarenal abdominal aorta.

Cytopathology

376 Cytologic Features of Thyroid Lesions Diagnosed as Indeterminate for Neoplasia Which Predict Follicular Neoplasm on Fine Needle Aspiration Biopsy of Thyroid (FNAB): A 5-Year Retrospective Study in a Tertiary Care Hospital in Ontario, Canada

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Background: Follicular lesions (FL) of the thyroid encompass non-neoplastic and neoplastic lesions. Diagnosis of follicular lesion is a challenging area in the interpretation