

of nodal disease. All four patients had a prior history of smoking. Three of four neoplasms were found in a setting of emphysema [pT1a (n=2) and pT2a (n=1)], and the fourth presented in a setting of interstitial pulmonary fibrosis (pT1a). Three of four patients are alive (as of October 2014) with no evidence of recurrence or metastasis. One patient died from causes unrelated to the malignancy detected in the explanted lung. In three cases, pre-transplant CT scan failed to identify any focal lesions and in one case, scarring was identified without any suspicion of malignancy.

**Conclusion:** Incidentally detected malignant neoplasms in explanted lungs at transplantation are uncommon. All carcinomas were detected in the last four years which is presumed to be due to a more extensive sampling. In this study set, squamous cell carcinoma was the most frequent malignancy. Imaging studies performed pre-transplant may not detect these incidental tumors due to the background of chronic lung disease. Although the presence of a pre-existing noplasm is considered a deterrent for transplantation, in this limited study, the behavior of these incidentally detected tumors seems to be rather indolent.

## 881

### Comparative Analysis of Distribution of Acute Cellular Rejection and Antibody-Mediated Rejection With Emphasis on Time After Heart Transplantation in Two European Transplant Centers

K. Wassilew,<sup>1</sup> T. Haberl,<sup>2</sup> A. Zuckermann,<sup>2</sup> K. Aumayr.<sup>3</sup> <sup>1</sup>Cardiac Pathology Unit, Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin, Berlin, Germany; <sup>2</sup>Cardiac Surgery Department, Medical University Vienna, Vienna, Austria; <sup>3</sup>Clinical Department of Pathology, Medical University Vienna, Vienna, Austria.

**Purpose:** We aimed to analyze whether differences in transplant frequency in two transplant centers may have an impact on the diagnostic setting, considering the frequency of acute cellular (ACR) and antibody-mediated rejection (AMR) with emphasis on the time distribution of the protocol endomyocardial biopsies (EMBs) after heart transplantation (HTx).

**Methods:** Retrospectively, we identified all consecutive EMBs of cardiac allografts taken between 07/2013 and 07/2014 in both centers [center A (A) with opt-out regimen for Tx: n=224 EMBs of 84 patients, center B (B) with opt-in regimen for Tx: n= 110 EMBs of 131 patients]. Patients with Re-HTx, multiple organ Tx, those transplanted at different than both centers and EMBs with insufficient tissue for diagnosis were excluded from statistical analysis. The age at HTx and time after HTx, the grade of ACR and C4d results were recorded. Statistical analysis was performed using SPSS (t-test and ANOVA).

**Results:** Although the patients in A were two decades older than in center B at time of HTx (mean age 52 and 32 years) there was a skew in distribution of EMBs with regard to time after HTx (A mean= 316 days, B mean= 2848 days). The data suggested different HTx frequency between centers, with a higher number in A, as over one third of EMBs were performed within 30 days after HTx (n = 70) in comparison to B (n =6, 4.5%). The opposite was true for EMBs taken more than 10 years after HTx (A: n = 9, 4%; B: n = 72, 55%). The distribution of ACR grades was nearly equal between the centers (0R= 75.9% vs 74%, 1R= 20.5% vs 25.2%, 2R=3.6% vs 0.8%, p=0.862). C4d positive cases were 4 times higher in B (n=2 vs 8, p=0.004).

**Conclusion:** Despite the disproportion in HTx numbers between the centers and probable variance in protocols for harvesting EMBs, the frequency of ACR and the distribution of ACR grades were nearly equal. The discrepancy in AMR (i) positive cases might be explained by the different size of patient cohorts. Our findings suggest that, with standardized immunosuppressive regimens, the frequency of ACR and AMR does not diverge significantly between countries.

## 882

### Cardiac Post-Transplant Biopsy Tissue Processing and Reporting Protocols for Rejection: A Comparative Survey of Routine Practice Across Three European Centres

A. Chaturvedi,<sup>1</sup> K. Aumayr,<sup>2</sup> K. Wassilew.<sup>3</sup> <sup>1</sup>Department of Histopathology, University Hospital of South Manchester (U.K.), Manchester, United Kingdom; <sup>2</sup>Clinical Department of Pathology, Medical University Vienna, Vienna, Austria; <sup>3</sup>Division Cardiac Pathology, Department of Cardiovascular and Thoracic Surgery, Deutsches Herzzentrum Berlin, Berlin, Germany.

**Purpose:** First developed by the International Society for Heart and Lung Transplantation (ISHLT) in 1990, the standardized grading method to determine acute cellular rejection (ACR) on endo-myocardial biopsy has since been reviewed and updated (2004). In 2013, the ISHLT issued a further consensus working formulation for the standardization of nomenclature towards pathological diagnosis of antibody-mediated rejection (AMR) in heart transplantation. This survey describes and compares current reporting protocols at three European cardiac transplant centres (Manchester; Berlin and Vienna). The objectives are to identify similarities and variations between the three centres and to compare working practices at these centres with respect to the consensus guidelines issued by the ISHLT. The overall aim is to highlight areas of good practice and identify any possible areas requiring modifications.

**Methods:** Detailed protocols with respect to processing (including tissue sectioning and staining) and reporting of antibody mediated rejection were collated from the three centres (see table 1).

**Results:** All three centres incorporate the recommended ISHLT 2004 reporting guidelines for assessment of acute cellular rejection with additional comment on the 1990 grade by at least one centre. Although a wide variation is noted in the range of antibodies being used, however, C4d is used at all three centres as recommended by the 2013 ISHLT guidance on AMR reporting. Special stains for collagen are not performed at one centre.

**Conclusion:** Overall, this survey highlights a largely similar approach to reporting practice across the three centres with evidence of a greater acceptance of the 2004 reporting guidelines. The general acceptance and implementation of standardized criteria and methodologies for diagnosing ACR and AMR allows for a more robust interpretation and improved correlation with diagnosis of rejection and patient management.

Summary comparison of transplant biopsy tissue processing and reporting practices at three centres

	ACR Grading method (ISHLT) [AMR -2013]	Collagen stains	IHC	IF	image analysis software
Berlin	2004;	Picrosirius red	CD3,CD68, CD31, Actin, Collagen 3, Collagen 4, C4d and fibrinogen	Not done	Yes
Manchester	2004	nil	CD31, C4d and CD68	Not done	no
Vienna	1990 and 2004	EVG	C3d and C4d	Not done	no

## 883

### Cytokine and MicroRNA Profiles of Ectopic Lymphoid Structures in Cardiac Allograft Vasculopathy

M. Huibers,<sup>1</sup> J. van Kuik,<sup>1</sup> S. Beerthuijzen,<sup>1</sup> E. Siera-de Koning,<sup>1</sup> N. de Jonge,<sup>2</sup> R. de Weger.<sup>1</sup> <sup>1</sup>Pathology, UMC Utrecht, Utrecht, Netherlands; <sup>2</sup>Cardiology, UMC Utrecht, Utrecht, Netherlands.

**Purpose:** Cardiac allograft vasculopathy (CAV) is often accompanied by the occurrence of Ectopic Lymphoid Structures (ELS) surrounding the affected coronary artery. In order to determine the function of these ELS, the expression of cytokines and microRNAs (miR) was analyzed. We selected cytokines typically expressed by immune cells shown to be present in ELS (JHLT, vol 33, nr.4S, april 2014, S315, #875) or could instigate the formation or maintenance of ELS. In addition, 5 miRs previously shown to be important in CAV (JHLT, vol 32, nr 4S, april 2013, S242, #666) were investigated.

**Methods:** Autopsy material from 10 HTx patients with ELS was selected. After laser microdissection, expression of selected cytokines (IL-2,-4,-6,-7,-10,-12,-17,-23, CD20, CXCR3,TNF- $\alpha$ ,TGF- $\beta$ ,IFN- $\gamma$ ) and miRs (miR-21, -146, 214, -223, -886) was determined using Q-PCR. Expression of these targets within the intima, media, adventitia and ELS was compared to elucidate local expression.

**Results:** Cytokine and receptor expression is higher in ELS than in other vessel layers. This effect is particularly seen in large extensive ELS (predominantly CD20, CXCR3, IFN- $\gamma$  and TGF- $\beta$ ). Interleukin-2, -4, -12, and -17

were expressed at extremely low levels. miR-21, -214 and -886 expression was significantly lower in ELS compared to intima. In ELS miR-146 showed a slightly elevated expression level compared to the intima and media.

**Conclusion:** The detected cytokine profile suggests active recruitment and proliferation of leukocytes within ELS. The absence of certain interleukins could be explained by immune suppression within these patients. The low expression of miR-21, -214, and -886 in ELS compared to intima, suggests their role is more important in CAV development than in ELS formation. miR-146 however, could have a potential role in ELS formation or maintenance. These data indicate that ELS formation is complex and could be either beneficial or detrimental to the graft.

## 884

### Early Detection of Cardiac Allograft Vasculopathy (CAV) With Optical Coherence Tomography (OCT) in Pediatric Heart Transplant Recipients - Comparison to Angiographic Assessment

*S. Schubert,<sup>1</sup> E. Wellenhofer,<sup>2</sup> B. Peters,<sup>1</sup> M. Kanaan,<sup>1</sup> F. Berger.<sup>1</sup>* <sup>1</sup>Dept. of Congenital Heart Disease/Pediatric Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany; <sup>2</sup>Dept. of Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany.

**Purpose:** Cardiac allograft vasculopathy (CAV) is the main cause of graft failure after pediatric heart transplantation (HTx). CAV might be detected by angiography or intravascular imaging, like Optical coherence tomography (OCT). This study compares angiography with OCT.

**Methods:** OCT was used in pediatric HTx-patients in addition to angiography during routine follow-up examinations. Angiography was judged according to ISHLT-criteria by a blinded cardiologist. OCT was analyzed and vessels were judged as normal, regional pathological or pathological. Vessel lumen area, diameter and layer were quantified.

**Results:** 24 patients were included during 2012-2014. Median age was 8.4 (4.6 - 12.1) years; median posttransplant time was 5.6 (4.5-11.4) years. CAV was judged positive in only 3/23 patients (2x grade 1 and 1x grade 2) according to ISHLT-criteria. OCT showed normal vessels in 5x, regional pathological changes in 9x and pathological changes in 10x patients. Vessel layer thickening (intima and media) was predominant and wall diameter to lumen area was a good indicator of pathological vessel structure.

**Conclusion:** CAV -hidden from angiographic assesment according to ISHLT-criteria - might be illuminated by OCT. As treatment might therefore start earlier clinical impact or progression needs to be underlined by graft survival and follow-up examinations.

## 885

### Do Pain and Withdrawal Issues Significantly Affect the Post-Transplant Recovery of Pediatric Ventricular Assist Device Recipients?

*D. Guadiz,<sup>1</sup> P. Shah,<sup>2</sup> J. Menteer,<sup>2</sup> M. Horn,<sup>2</sup> D. Dechant,<sup>2</sup> C. Buckley,<sup>2</sup> S. Turkel,<sup>2</sup> I. Brook,<sup>2</sup> C. Herrington,<sup>2</sup> J. Szmuszkovicz.<sup>1</sup>* <sup>1</sup>Cardiothoracic Transplant, Children's Hospital Los Angeles, Los Angeles, CA; <sup>2</sup>Children's Hospital Los Angeles, Los Angeles, CA.

**Purpose:** While pediatric ventricular assist device (VAD) support successfully bridges children to heart transplant (tx), patients (pts) often endure prolonged hospitalizations waiting for an organ donor. Surgery and other procedures requiring opiates and sedative medications (meds) lead to withdrawal issues. We examined the pre-and post-tx data for our center's VAD population to assess how pain and withdrawal affected their post-tx course.

**Methods:** We reviewed records for pts who underwent VAD implantation at our center between 2009 and 2014. We analyzed demographics, pain and withdrawal scores, and meds. We compared post-tx length of stay (LOS) of VAD pts to non-VAD pts transplanted during the same period. Results were reported in median and interquartile range (IQR). Average was calculated for each pt's scores by the number of times assessed each day. Median was calculated from the average scores of all patients.

**Results:** 11 Berlin Heart VADS were implanted; all for dilated cardiomyopathy. 55% were male, 45% female. All pts survived to transplant. 27% required ECMO pre-VAD. Median age at VAD implant was 91 (5-137) months. Median duration of hospitalization was 8 (3-9) months. VADS remained implanted for 144 (49-211) median days. Pain and withdrawal assessments are shown in Table 1.

Post-tx (LOS) was not significantly different in VAD pts. versus non-VAD pts (p=0.31). Post-tx median LOS=24 (17-33) days for 11 VAD tx pts. Post-tx median LOS=18 (12-24) days for 13 non-VAD tx pts. 92% of pts were discharged home without a methadone taper.

**Conclusion:** Despite prolonged hospitalization, medical procedures, and the use of multiple medications, pediatric VAD pts at our center did not experience pain and withdrawal issues that significantly affected their post-tx recovery.

Table 1: Pain and Withdrawal Data (n=11)

	Pre-transplant		Post-transplant	
	N (%)	Median (IQR)	N (%)	Median (IQR)
<b>Pain Scores</b>				
Average FLACC Score (Face, Leg, Activity, Cry, Consolability)	11(100)	1.24 (0.97-1.39)	11(100)	1.17 (0.91-1.75)
Average FACES Score	6 (55)	1.76 (1.27-2.16)	6 (55)	1.43 (1-1.74)
Average Verbal Score	7 (64)	2.09 (1.24-3.01)	6 (55)	1.86 (1.01-2.29)
Average Sedation Score	9 (82)	1.13 (0.88-1.51)	9 (82)	0.79 (0.66-0.88)
<b>Pain/Sedation Meds (Days)</b>				
Fentanyl	10(91)	9 (4-14)	11 (100)	2 (2-3)
Dilaudid	7 (64)	65 (38-137)	4 (36)	8 (5-28)
Morphine	10 (91)	20 (11-31)	8 (73)	5 (4-6)
Oxycodone	2 (18)	16 (3-29)	2 (18)	3 (1-4)
Ativan	11 (100)	20 (16-50)	11 (100)	3 (2-7)
Versed	2 (18)	27 (17-36)	1 (9)	2 (2-2)
<b>Withdrawal Score</b>				
WAT-1 (Withdrawal Assessment Tool- Version 1)	4 (36)	2.48 (2.01-2.7)	2 (18)	2.02 (1.43-2.6)
<b>Withdrawal Meds (Days)</b>				
Clonidine	4 (36)	117 (52-188)	3 (27)	7 (6-115)
Methadone	3 (27)	141 (28-205)	2 (18)	61 (35-87)

## 886

### Somatic Growth in Children With Ventricular Assist Device Support

*C.J. Vander Pluym,<sup>1</sup> K.R. Schmitt,<sup>2</sup> B. Hawkins,<sup>1</sup> J. Voelkner,<sup>2</sup> O. Miera.<sup>2</sup>* <sup>1</sup>Cardiology, Boston Children's Hospital, Boston, MA; <sup>2</sup>Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany.

**Purpose:** Feeding intolerance, anorexia and failure to thrive are common manifestations of heart failure in children. Inability to gain weight on maximal medical heart failure therapy and nutritional support may prompt more advanced interventions such as implantation of ventricular assist devices (VAD). While it is assumed that VADs will improve patient's symptoms of heart failure, little is known about the effects of VADs on somatic growth. We sought to define somatic growth patterns for children with VADs.

**Methods:** All patients aged  $\leq 18$  years of age at time of VAD implantation at 2 institutions (Boston Children's Hospital, Deutsches Herzzentrum Berlin) were reviewed from 2005-2014. Only patients that were supported more than 14 days were included. Demographic data at time of VAD implantation was collected. Weight and heights at time of VAD implantation and at time of explantation due to transplantation, weaning or death were recorded and converted to z-scores. Failure to thrive (FTT) was defined as a z-score  $\leq -2.0$  for weight.

**Results:** Over 10 years, 101 patients (female 53), aged  $2.53 \pm 2.43$  years (median 1.30; 0.03 to 19.9 years) underwent implantation of VADs; 71 LVAD (55 Berlin Heart®, 16 HeartWare®), and 30 BiVADs. Diagnosis at time of implant included; cardiomyopathy (75), myocarditis (6) and congenital heart disease/post cardiopulmonary bypass (20). Total days of VAD support was 12,708, with a median duration of 60 days (range 14 to 882 days). At time of VAD implantation, 38 patients (37.6%) were defined as FTT based on a z-score for weight  $\leq -2.0$ . The majority of these patients had cardiomyopathy (n=27). The mean weight at time of implant was  $23.1 \pm 22.1$  kg (median 13.4, range 3.6 to 100 kg), with a median z-score of -1.2 (-4.9 to 3.0). The mean weight at time of explant or last clinic visit was  $24.2 \pm 23.1$  kg (median