after heterotopic heart transplantation in a murine model. Using the technique of macroarrays and immunohistochemistry, we have shown that MIP-1β was over expressed and that VE-Cadherin was under expressed in the endothelial cells (ECs) of rejecting allografts. In this study, routine endomyocardial biopsies were performed following human heart transplantation. Cardiac tissues were embedded in paraffin for routine histologic analysis. Specimen was graded for AR using the "ISHLT" criteria. Immunohistochemical staining for the expression of MIP-1β and VE-Cadherin was performed in cardiac tissues showing either no rejection (n=10), rejection grade IB (n=10), or rejection grade IIIA (n=10).
Results: MIP-1β was strongly expressed (+++) on ECs in heart tissues showing an AR grade IIIA when compared to heart tissue showing grade IB (++) AR or cardiac tissues with no AR (+). VE-Cadherin was detected as a thin, linear staining on ECs in cardiac tissues showing no rejection (+++ or strongly positive). In contrast, the VE-Cadherin staining was weak (+ or weakly positive) or completely absent on ECs present in biopsies showing AR (grade IB and IIIA).
Conclusions: We have identified and validated for the first time 2 genes (MIP-1β and VE-Cadherin) present in ECs lining the vessel walls, as markers of AR in human cardiac tissues. MIP-1β, a chemokine, induces chemotaxis and adhesion of T-cells on ECs; VE-Cadherin, an endothelial-specific membrane protein responsible for the endothelial cell-cell adhesion, plays a key role in the migration of lymphocytes into myocardial tissues. Validated genes derived from the murine model can be used as potential targets in AR in human heart transplantation.

1185-60 Post-Transplant Cardiac Rejection Monitoring With and Without Routine Biopsy Screenings: Comparison of Two Different Surveillance Strategies

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Background: Rejection surveillance is extensively based on routine endomyocardial biopsy (EMB) screenings. Nevertheless, routine EMBs are distressing to the patients and risky. To verify the possibility to replace routine EMB screenings by efficiently timed diagnostic EMBs, we compared the diagnostic efficiency of routine EMBs with that of a combined, mainly non-invasive rejection surveillance-strategy, in which EMBs were performed optionally, only in patients suspected for rejection.
Methods: Two groups of patients underwent different rejection surveillance strategies during their first post-transplant year. In group A (n =76) we performed a telemetric monitoring of the intramyocardial electrogram (IMEG) from a dual-chamber pacemaker. Overnight IMEG changes were analyzed on daily printouts. Additional pulsed-wave tissue Doppler (PW-TD) wall motion analyses were performed daily during hospitalization and after discharge, at each ambulatory examination. In group B (n =22), additionally to IMEG recordings and PW-TD examinations, independent routine EMB screenings were performed at predefined time intervals.
Results: In group A the mean number of EMBs per patient (1.45 ±1.25) was 88.9% lower than the number of routine EMBs performed in each patient of group B. In group A, 21.1% of the patients had no relevant IMEG and/or PW-TD changes and therefore no EMBs. The average numbers of rejection therapies per patient performed in group A (0.74 ±0.71) and group B (0.77 ± 0.75), as well as the number of morphological significant (ISHLT grade > 2) rejection episodes per patient (0.16 ± 0.15) in group A and 0.14 ± 0.13 in group B) were similar. In group B 93.6% of the routine EMBs had no therapeutic consequences. In group A, 50.9% of rejection episodes, suspected by IMEG and/or PW-TDI changes and confirmed by EMBs, were clinically relevant and needed antirejection treatment. No patient died during the study.
Conclusions: Non-invasive rejection surveillance based on IMEG recordings and tissue Doppler wall motion analyses in combination with diagnostic EMBs allow a reliable, efficient and save monitoring even during the first post-transplant year, without unnecessary and distressing routine EMBs.

1185-61 The Utility of Surveillance Endomyocardial Biopsies in Detecting Cellular Rejection in Pediatric Heart Transplant Patients

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Background: Routine surveillance endomyocardial biopsies (EMB) are commonly used to screen for cellular rejection in pediatric heart transplant patients. With advances in immunosuppression, the benefit of EMB in asymptomatic pediatric heart transplant patients is unclear.
Methods: After orthotopic heart transplant (OHT), surveillance EMBs were routinely performed on all pediatric OHT patients with decreasing frequency. All biopsy specimens were reviewed by a cardiac pathologist, and graded according to International Society for Heart and Lung Transplantation (ISHLT) guidelines. A retrospective review of consecutive EMBs performed at our institution from January 1995 to September 2002 was conducted. The echocardiogram results, clinical history and treatment changes at the time of every biopsy were also recorded.
Results: Results of 866 EMBs from 91 patients were reviewed. Two hundred and thirty-seven EMBs (23.9%) were performed within thirty-days of OHT, 394 EMBs (45.5%) were performed between one month and one year from OHT, and 265 EMBs (30.6%) were performed more than 1 year after OHT. Of all EMBs, 1.39% were ISHLT grade 2 or higher, 3.58% were grade 1B, 19.4 % were grade 1A, and 74.6% were grade 0. Six of the EMB were unable to be interpreted because of insufficient tissue. Of the twelve patients in whom the EMB was read as grade 2 or higher, six were less than one month from OHT and asymptomatic. The other six patients with greater than 1B cellular rejection presented for biopsy because of symptoms and had abnormal function on echocardiogram. Of the 820 EMB performed in asymptomatic patients more than one month from OHT, there were no episodes of cellular rejection greater than 1B. There were 21 asymptomatic patient biopsies (2.56%) with grade 1B rejection. All grade 1B rejection detected by surveillance EMB resolved in both treated and untreated cases.
Conclusion: EMB should only be used to screen for cellular rejection in the first month after pediatric heart transplantation. For pediatric patients more than thirty days after OHT, EMB has failed to reveal significant episodes of cellular rejection in asymptomatic patients. The utility of surveillance EMB to detect humoral rejection was not assessed.

1185-84 Rejection Surveillance Late After Heart Transplantation

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Although routine endomyocardial biopsies (EMBs) continue to detect cardiac rejection (CR) beyond the first post-transplant year, their need for late CR surveillance is controversial. However, late CRs are associated with both graft failure and allograft coronary disease (ACD). To provide appropriate CR surveillance during late post-transplant periods, we assessed the usefulness of non-invasive screenings for both CR diagnosis and effective use of EMBs.
Methods: In 130 patients (post-transplant times: 2– 15 years) monitored routinely by tissue Doppler imaging (TDI), we compared the diagnostic efficacy of routine EMBs (performed unrelated to TDI results) with that of diagnostic EMBs (timed by TDI). Routine EMBs were performed in 98 patients during annual follow-up catheterizations. Diagnostic EMBs, conducted whenever TDI detected left ventricular wall motion alterations (prolongation of relaxation time and/or reduction of systolic and/or diastolic peak velocities), were performed in 32 patients.
Results: Most routine EMBs (89.9%) were ISHLT grade 0 and TDI performed before showed no CR relevant changes. CRs grade 1A and 1B were shown in 8.1% of routine EMBs. Two routine EMBs (2%), obtained from 2 asymptomatic patients with TDI changes, showed relevant CRs grade 3A. Among the 38 diagnostic EMBs performed due to TDI alterations in 32 patients, 7 (18.4%) were ISHLT grade 0, but in 5 cases the coronary angiogram showed either new appearance or aggravation of ACD. The other 31diagnostic EMBs showed cellular CRs of different degrees (32.3% 1A and 1B, 9.8% grade 2, 57.9% 3A and 3B). Vascular reactions were detectable in 22 diagnostic EMBs. Reduction with >15% of systolic velocity Sm, evident in 81.8% of all patients with CR, was shown in all patients with clinically relevant CRs (ISHLT ≥ grade 2 plus 1A and 1B accompanied by hemodynamic deterioration and/or vascular rejections).
Conclusions: Routine annual EMBs detect only a fraction of relevant CRs which occur late after transplantation. Serial TDI screenings followed by diagnostic EMBs, whenever relevant wall motion alterations are detected, increase the efficacy of CR diagnosis and provide a tempting strategy for late post-transplant CR surveillance.

1185-85 Noncultured Autologous Skeletal Muscle Cells Can Successfully Engraft in Ovine Myocardium

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Background: The concept of myogenic cell transplantation into the myocardium, known as cellular cardiomyoplasty (CCM), is based on the contribution of exogenous cells to replace lost or altered cardiomyocytes in order to restore functional performances of the heart. There is a large body of evidence showing that CCM performed with skeletal muscle cells can improve cardiac function in ischemic heart disease as well as dilated cardiomyopathy on numerous animal models. Most research teams have addressed autologous CCM in a three phase process : biopsy, ex vivo cell culture/expansion and surgical or catheter based cell delivery. Considering the potential benefit of using non cultured muscle cells (little time, lower cost, reduced risk of contamination), we investigated the feasibility of grafting cells obtained directly after enzymatic dissociation of skeletal muscle biopsies in ovine myocardium.We hypothesized that those non cultured muscle cells would massively engraft. Methods: Autologous intramyocardial skeletal muscle cells implantation was carried out in 8 sheep. A skeletal muscle biopsy (about 10 g) was explanted from each animal. The sheep were left to recover over approximately three hours and reanesthetized when the cells were ready for the implantation. A left fifth intercostal thoracotomy was performed and 10 epicardial injections of the muscle preparation (between 10 and 20 million cells) were carried out. All sheep were euthanized 3 weeks after myocardial implantation. Immunohistochemistry was performed with monoclonal antibodies to a fast skeletal isoform of myosin heavy chain. Results: Skeletal myosin heavy chain expression was detected in all slides at 3 weeks after implantation in 8 of 8 animals, confirming engraftment of skeletal muscle cells. Massive areas of engraftment (from 2 to 9 mm in diameter) or discrete loci were noted within the myocardial wall. Conclusions: In conclusion, our results indicate that non-cultured skeletal muscle cells can successfully and massively engraft in ovine myocardium. Thus, skipping the cell culture expansion phase is feasible and could become a promising option for cellular cardiomyoplasty.

1185-86 Combination of Mesenchymal Stem Cell Transplantation and Angiogenic Gene Transfer for Myocardial Regeneration and Therapeutic Angiogenesis

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Bone marrow-derived stem cells including mesenchymal stem cells (MSCs) have attracted attention as potential platforms for the delivery of therapeutic genes. Lentiviral vectors are promising tools for the development of gene therapy since they can transduce both quiescent and dividing cells. We have previously demonstrated that MSCs can be differentiated into cardiomyocytes and restoration of blood flow is crucial for the fate of