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Purpose: We evaluated outcomes of orthotopic heart transplantation (OHT) using donors with left ventricular hypertrophy (LVH) and assessed changes in LV wall thickness in patients who received a donor hearts with or without LVH.

Methods and Materials: We reviewed 427 patients who had OHT: 62 received hearts with LVH (interventricular septum (IVS) or posterior wall (PW) thickness ≥12 mm) by echocardiography and 365 patients without donor LVH.

Results: Mean recipient age was 56±11 and donor age 30±2 yrs. Recipient age, gender, UNOS status, indications for OHT, and hemodynamics were similar in both groups. Ischemic time >240 min occurred only in patients with LVH (6%, p=0.03). The mean donor age was greater in the LVH group (35±12 vs 29±12, p=0.001) and they had higher rates of intracranial hemorrhage (38% vs 15%), p=0.001). Other donor characteristics were similar. LV wall thickness (LVWT) was increased in the LVH group compared with non-LVH donors (IVS: 12.6±1.9 vs 8.5± 1.1, PW: 12.7± 1.0 vs 9.0±1.0 mm, p=0.0001). Mild LVH (LVWT 12-13 mm) was found in 42%, moderate (>13-17 mm) in 53% and severe (>17 mm) in 5% of donors. Median follow-up was 3.8 yrs (range 0 to 17 yrs). Significant regression of LVH occurred (IVS: -1.6± 2.0 mm, p=0.0004, PW: -1.8± 0.2 mm, p=0.001) at mean followup of 4±2 yrs. The mean IVS: 1.1± 0.2 vs 1.1± 0.1,p=0.2 , PW: 1.1± 0.2 vs 1.1±0.1,p=0.5 and rates of patients with LVH (38% vs 32%, p=0.5) were similar in both groups at followup. Recipients of hearts with and without LVH had similar 30 day (1.6% vs. 3.3%, p=0.7) and 1 yr mortality (3.5% vs 9.5%,p=0.2). Long-term survival was similar in the two groups, p=0.11; survival estimates (7 yrs) were 66±1% vs 57±3%. The incidences of rejection and graft CAD were similar in the two groups. Multivariate analysis revealed no evidence that donor LVH was associated with increased mortality.

Conclusions: Short- and long-term survival , LV wall thickness and rates of LVH at follow-up were similar in both groups, suggesting that donor hearts with mild and moderate LVH can be successfully used in OHT.

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WITHDRAWN

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THREE-DIMENSIONAL MATRIX EMBEDDING OF ENDOTHELIAL CELLS ABATES ALLOIMMUNITY VIA UPREGULATION OF $CD4^+CD25^+FOXP3^+$ T REGULATORY CELLS

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Purpose: Recent evidence suggests that endothelial cells (EC) actively regulate immune responses, yet factors that determine whether EC suppress or activate naïve host immune cells need to be further elucidated. Interactions of EC with the three-dimensional (3D) extracellular matrix regulate important EC functions. As EC removal from the native 3D environment alters biochemical and mechanical signaling responsible for maintaining vascular quiescence we hypothesized that culture of human aortic EC (HAE) in a more realistic 3D milieu in place of 2D monolayers would procure suppressive over stimulating EC immune properties.

Methods and Materials: The ability of HAE grown 2D on tissue culture plates to induce immunosuppressive $CD4^+CD25^+Foxp3^+$ and expansion of effector T cells was compared with HAE surface-adherent to 3D collagen-based matrices using RT-PCR, flow-cytometry, and ELISPOT.

Results: EC morphology and secretion of heparan sulfate proteoglycans, nitric oxide and TGF-β confirmed confluence of 3D-HAE. 3D-embedding conferred EC immune quiescence evidenced by weak cytokine-induced expression of costimulatory and MHCII molecules ($p<0.001$ vs. 2D-EC). 3D-HAE induced 6-fold lower IFN-γ- and IL-2-expressing effector T cells than 2D-HAE ($p<0.005$), whereas induction of immunosuppressive $CD4^+CD25^+Foxp3^+$ T was significantly augmented (15±1 vs. 9±1%; $p<0.02$). Increased ratio of immunosuppressive:immunoreactive T cells induced by 3D-HAE resulted in a 6-fold reduced $CD4^+$ T cell proliferation to allogeneic EC ($p<0.001$).

Conclusions: It is increasingly appreciated that 3D cell culture offers a more realistic milieu to study cellular physiology. We now demonstrate that matrix architecture is critical for EC immunogenicity: 3D environment dampens *in vitro* alloimmunity to HAE via upregulation of suppressive T regulatory cells. Our findings might enhance our understanding how EC actively regulate immune responses and provide insights how EC-matrix interactions might contribute to acceptance/rejection of vascularized grafts.

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THE PULMONARY MILIEU FACILITATES ALLOGRAFT AIRWAY REJECTION: A POSSIBLE ROLE FOR BRONCHUS ASSOCIATED LYMPHATIC TISSUE (BALT)

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Purpose: Graft locations remote from the pulmonary milieu have been a limitation of heterotopic tracheal transplant models of OB. The impact of pulmonary milieu on graft rejection was studied.

Methods and Materials: An intrapulmonary(IP) tracheal transplant model, where the donor trachea is implanted into the recipient pulmonary parenchyma, was compared to the standard subcutaneous(SC) transplant model. Minor antigen mismatched male-to-female(MF) allotransplants and female-to-female(FF) isotransplants in BN rats were used.

Results: Only MFIP transplants showed significant graft occlusion at d21 (mean±SEM, FFSC:13±1.2%, MFSC:13±0.9%, FFIP:22±7.9%, MFIP:83±8.0%*, $p<0.001$) with T cell($p<0.001$) and B cell($p<0.001$) infiltration documented by qRT-PCR. Flowcytometry demonstrated:1) increase in $CD11b^+$ neutrophil/monocyte in the recipient lung of MFIP and FFIP at d7 and 21, but not in the subcutaneous tissue of MFSC or FFSC; 2) activation of dendritic cells with upregulation of MHC II, CD80 and CD86 only in the lung of MFIP at d7, 3) activation of CD4+T cells and increase in CD8+T cells only in MFIP at d21. At d7, multiple BALT-like structures were seen in the lung tissue distant from the grafts both in MFIP and FFIP with similar size and number (morphometric quantification), but not in the subcutaneous tissue of MFSC or FFSC. At d21, BALT-like structures persisted in MFIP, but they returned to the normal lung level in FFIP($p=0.002$ size, $p=0.006$ number). FITC-dextran, injected in the graft at d12, was seen phagocytosed in the BALT-like structures 48 hours later, corroborating their functional role. BALT-like structures were also observed in a MHC mismatched model.

Conclusions: In tracheal transplant models of OB, pulmonary milieu facilitates allograft rejection with formation and maintenance of BALT-like structures in the native lung. The intrapulmonary model is likely an improved model since it includes the influences of innate and adaptive immunity particular to the pulmonary milieu and their link partly mediated by the BALT-like structures.