Monday, March 4, 1991
4:00PM–5:30PM, Room 257, West Concourse
Basic Research in the Transplant Setting

4:00

IL-1 INHIBITS ß-ADRENERGIC RESPONSIVENESS IN INTACT HUMAN VENTRICULAR MYOCARDIUM.

Robert J. Wiechmann, Mary Wollmering, Michael R. Bristow, University of Utah, Salt Lake City, UT

Previous studies in cultured heart cells have suggested that cytokines may inhibit ß-adrenergic receptor responsiveness. To test this hypothesis in human myocardium we incubated isolated RV trabeculae from six human hearts with idiopathic dilated cardiomyopathy in 10 U/ml recombinant interleukin-1ß for 4 hours. Contractile responses to isoproterenol (ISO), calcium (Ca^{2+}) and forskolin were measured in a multichamber tissue bath using trabeculae from end stage failing human hearts. Total ß-receptor density was measured using ^{125}[I]-ICYP binding. Results are % of control ±SEM:

	Muscle Contraction			ß-Receptor Density
	ISO	Ca^{2+}	Forskolin	
IL-1	62±8	88±1	92±14	119±14
p value	.009	NS	NS	NS

The ISO response of the IL-1 incubated group is decreased despite a maintained ß-receptor density and preservation of Ca^{2+} and forskolin responses, indicating that IL-1 uncouples ß-adrenergic receptors in human heart. Conclusion: IL-1 may be involved in the impairment of cardiac function that accompanies myocarditis or allograft rejection, via a post-receptor effect on the ß-receptor-adenylate cyclase complex.

4:15

THE ISOLATED SUPPORTED HUMAN HEART: A NOVEL MODEL FOR THE STUDY OF NEW DIAGNOSTIC AND THERAPEUTIC MODALITIES

Kamuran A. Kadipasaoglu, Ger B. Bennink, Jeff L. Conger, Steven M. Parnis, James J. Ferguson, O. H. Frazier, Texas Heart Institute, Houston, Texas

The purpose of this study was to develop a supported human heart model for use in future studies of new invasive diagnostic and therapeutic modalities targeted at the human coronary circulation. Preliminary experiments were performed using hearts from minipigs and mongrel dogs. Following cold cardioplegic arrest, the hearts were removed and connected via aortic cannulation to a modified Langendorff coronary perfusion circuit. Electrical activity was monitored with surface electrodes. Cardioplegia and hypothermia were then reversed with normothermic coronary perfusion of oxygenated autologous blood. Six animal hearts developed regular spontaneous contractions associated with electrical activity and were supported for an average of 100 minutes. When the perfusate was modified to include 1 ml/mg tissue/h of glucose-insulin-potassium solution (GIK), a 7th animal heart remained viable for 5 hours. We then proceeded to support 4 native human hearts (2 ischemic, 1 viral myocarditis, 1 idiopathic cardiomyopathy), cardioplegically arrested and excised from cardiac transplant recipients, using type-specific human donor RBC's in lactated Ringers (1:1) and GIK as perfusate. Myocardial contractility was successfully sustained for an average of 94 min (range 75-120). Pump flow necessary to maintain a coronary perfusion pressure of 80 mm Hg ranged from 500 cc/min to 1150 cc/min, corresponding to 75-150 cc/min/gm of cardiac tissue. *Ex vivo* myocardial oxygen consumption approached 50%. Left ventricular contraction pressures (against intraventricular balloons internally pressurized to 75 mm Hg) reached 35 mm Hg.

Conclusion: We have demonstrated the feasibility of an *ex vivo* supported human heart model. This model is potentially applicable to the preclinical evaluation of a wide variety of new interventional diagnostic and therapeutic techniques targeted as the human coronary circulation such as lasers, stents, mechanical atherectomy devices, and intravascular ultrasound.

4:30

ELEVATION OF SOLUBLE INTERLEUKIN-2 RECEPTORS DURING REJECTION IN CARDIAC TRANSPLANT RECIPIENTS

Howard J. Eisen, Sheri Belland, Ralph Nader, Rebekah Mull, William Kussmaul, Verdi DiSesa, University of Pennsylvania, Philadelphia, PA

Cardiac allograft rejection (R) is mediated by activated T lymphocytes. These cells secrete soluble interleukin-2 receptors (sIL2R). To determine if sIL2R from peripheral blood can be used to noninvasively detect R, 261 blood samples were obtained from 40 cardiac transplant recipients at the time of endomyocardial biopsy (Bx). All transplant recipients with infections or receiving steroid or antibody immunotherapy for R at the time of Bx were excluded. sIL2R levels were quantitated using a double antibody ELISA technique with spectrophotometric measurements and were expressed as units/ml. sIL2R levels were compared to histologic severity of R from Bx:

Bx	sIL2R (±SEM)
moderate/severe R	1110 ± 142 (n=43)*+
mild R	695 ± 57 (n=87)**
no R	523 ± 29 (n=130)

*p<0.0001 vs. no R; +p<0.002 vs. mild R;
**p<0.01 vs. no R

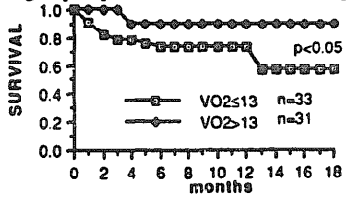
The negative predictive value for R for a sIL2R level <500 units/ml was 94%. We conclude that peripheral blood sIL2R can help distinguish R from no R and may be a useful adjunct to Bx.

4:45

MEASUREMENT OF MAXIMUM OXYGEN UPTAKE IS OF VALUE IN THE SELECTION OF PATIENTS FOR CARDIAC TRANSPLANTATION

Alan H. Singer, Randall H. Vagelos, Kathy Willson, Mary Nejedly, Michael B. Fowler, Stanford Univ. Medical Center, Stanford, CA

The selection of patients (pts) for cardiac transplantation is based on imprecise criteria. In order to evaluate the contribution of symptom limited exercise testing in the selection process, we examined data from all 139 adult pts seen at our institution for consideration for cardiac transplant in 1989. 98 of these pts had a baseline exercise test with analysis of gas exchange and 64 of those were not transplanted. There was no significant difference in age, sex, etiology of heart failure (CHF), or maximum oxygen uptake (VO2) in pts transplanted versus pts not transplanted. The median VO2 was 13 ml/kg/min. Survival (%±SEM), of pts not transplanted, with a VO2>13 was 90±5 at 6, 12, and 15 months. Survival of pts with VO2≤13 was 73±8, 73±8, and 57±11 at 6, 12, and 15 months respectively. The survival curves of the two groups were significantly different with p<0.05 by the log rank test. There were no significant differences in age, sex, or etiology of CHF in the group of pts with VO2≤13 versus the group with VO2>13.



Conclusions: Pts referred for cardiac transplantation, who have a VO2>13, have a short term survival equal to or better than that with transplantation, and therefore transplantation may be safely delayed. Pts with a VO2≤13 have a significantly worse short term prognosis and should be given priority for cardiac transplantation.