PV tree was developed where pressure was modeled as the product of chamber elastance and volume. An analytical solution of the unsteady Bernoulli equation was achieved by linearizing the equation. The solution equation consisted of a cosine function, which captures *vis a tergo*, and a sine function, which captures *vis a fronte*. Time-varying systolic PV velocity, ut(t) – cms, is a function of the following variables: total atrial suction created by atrial relaxation (ΔP_{ar} – mmHg) and mitral annular descent (ΔP_{md} – mmHg), atrial (E_a – mmHg/cc) and PV elastance (E_{pv}), net atrial – PV elastance ($E_{net} = E_a + E_{pv}$), the average rate of PV tree replenishment from the capillaries (Q_L – cm^3/s), total PV cross-sectional area at the atrial junction (A – cm^2), and PV inertance (pL_{eff} – g/cm^2). This model found that the peak velocity and integral of systolic PV flow increased as atrial suction and PV tree replenishment increased, but decreased as atrial and PV elastance, PV inertance, and PV cross-sectional area increased. Also, this model predicts aspects of systolic PV flow that are consistent with experimental and clinical observations: (i) the *vis a tergo* component of systolic PV flow is minimized by compliant PVs (small PV elastance); (ii) atrial events, so-called *vis a fronte*, dominate the magnitude of systolic PV flow; (iii) systolic PV flow is reduced by elevations in atrial pressure but *only* when compliance is also reduced; (iv) compensatory increases in atrial suction and PV tree replenishment may overcome reductions in systolic PV flow due to elevated atrial pressures; (v) PV inertance and area are important determinants of the magnitude and timing of PV flow.

$$U(t) = \frac{Q_L E_{pv}}{E_{net} A}\left[1 - \cos\sqrt{\frac{E_{net} A}{\rho L_{eff}}}(t)\right] + \frac{\Delta P_{ar} + \Delta P_{md}}{\sqrt{\rho L_{eff} E_{net} A}} \sin\sqrt{\frac{E_{net} A}{\rho L_{eff}}}(t)$$

11:15

407-4 Differential Sympathetic Neural Control of Muscle Oxygenation in Resting and Exercising Human Skeletal Muscle

Jim Hansen, Gail D. Thomas, William J. Parsons, Ronald G. Victor. *UT Southwestern, Dallas, Texas*

Although the muscle metaboreflex triggers increases in muscle sympathetic nerve activity (SNA) targeted to both resting and exercising human skeletal muscle, our recent rat studies advance the hypothesis that the vasoconstriction normally evoked by increased muscle SNA is selectively attenuated in the contracting muscle, thereby optimizing muscle perfusion. The ability to continuously measure muscle oxygenation (cytochrome a,a_3 redox state and tissue oxygen stores ($t(HbO_2 + MbO_2)$) in exercising muscle with near infrared spectroscopy while simultaneously measuring muscle SNA (microneurography) provided a new opportunity to test this hypothesis in humans. Specifically, we asked if a reflex increase in muscle SNA decreases muscle oxygenation in resting, but not in exercising muscle. In 10 healthy humans, we measured oxygenation in forearm muscle during reflex increases in muscle SNA evoked by non-hypotensive lower body negative pressure (LBNP, –20 mmHg) at rest and during mild rhythmic handgrip (5 min 20% of maximum). At rest, LBNP increased muscle SNA by 292 ± 72% (mean ± SE) and decreased $t(HbO_2 + MbO_2)$ by 10 ± 1% ($p < 0.05$) of the maximal decrease (assessed with complete forearm ischemia). This decrease in $t(HbO_2 + MbO_2)$ in the resting forearm was sympathetically-mediated because it was abolished by local sympathetic block with bretylium. Handgrip alone caused no change in muscle SNA, but rapidly decreased $t(HbO_2 + MbO_2)$ to a steady state 28 ± 4% below baseline. Importantly, when superimposed on handgrip, LBNP increased MSNA by 305 ± 59%, but now had no effect on tissue oxygenation in the exercising muscle ($\Delta t(HbO_2 + MbO_2)$ = +0.4 ± 3%, p = ns). These data provide direct evidence in humans that reflex sympathetic activation decreases oxygenation in resting, but not in exercising human skeletal muscle. This mechanism would optimize oxygenation of active muscle when the muscle metaboreflex is engaged.

11:30

407-5 The Pharmaco-Genetics of Congenital Cardiac Defects in Retinoic Acid Receptor Deficient Mouse Embryos

Henry M. Sucov, Vicky LaMorte, Jiangming Luo, Vincent Giguere, Ronald M. Evans. *Univ. of Southern California School of Medicine, Los Angeles, CA*

Germline mutations in several of the genes which encode receptors for the signaling molecule retinoic acid (RA) have been previously established in mice. Cardiac phenotypes which emerge in mutant embryos include defects in the ventricular chamber, conus, truncus, and aortic arch arteries. Based on new experimental and theoretical observations, the following conclusions have been drawn concerning the pharmacology of RA receptor function in mediating complex aspects of cardiac morphogenesis: (1) the level of functional receptor, known to be a heterodimer of RAR and RXR monomers, is dictated by equilibrium considerations; (2) in the tissue involved in septation of the truncus, the levels of RAR and RXR monomers are roughly comparable, explaining the emergence of persistent truncus arteriosus only after combined mutation of RAR and RXR; (3) target genes of RA action critical in the morphogenesis of the ventricular chamber contain receptor binding sites in their promoters of moderate, rather than high, affinity; this is also likely to be true in most other cases of RA action; (4) differentiation of the conus cushions is a significantly different response to RA than is morphogenesis of either the truncus or the ventricular chamber, in that the conus is sensitive to both insufficient or excess RA, whereas the truncus and ventricular chamber are sensitive to only RA deficiency; (5) the pharmacology of the RA receptors may in some cases make it possible to reverse the consequences of receptor mutation by treatment with exogenous RA; this approach was not successful in rescuing the hypoplastic ventricular phenotype, indicating that receptor mutation also supresses the inducible RA response to below the required threshold in this tissue. These conclusions make testable predictions concerning the molecular mechanisms of normal and pathological cardiac morphogenesis, which will be evaluated through future molecular analysis.

Discussion 11:45

408 Young Investigators Awards Competition – Molecular and Cellular Cardiology

Monday, March 25, 1996, 2:00 p.m.–3:30 p.m.
Orange County Convention Center, Room 231

2:00

408-1 Localization of the Gene for Familial Idiopathic Dilated Cardiomyopathy to Chromosome 1q32

Jean-Bernard Durand, Linda L. Bachinski, Lisa Beiling, Grazyna Z. Czernuszewicz, Antoine B. Abchee, Qun Tao Yu, Rita Hill, Jonah Ifegwu, A.J. Marian, Ramon Brugada, Steven Daiger, Jane M. Gregoritch, Jeff Anderson, Miguel Quiñones, Jeffrey A. Towbin, Robert Roberts. *Baylor College of Medicine, Houston, Texas*

Cardiac failure is the fastest growing cardiovascular condition in the Western world with over 400,000 new cases per year in the U.S. The cost in the U.S. for cardiac transplantation alone is over $200 million and for all cardiac failure over $10 billion. Dilated cardiomyopathy (DCM), the most common cause of heart failure, is a primary cardiac disease characterized by ventricular dilatation and impaired systolic contraction and manifested clinically by either sudden death or pump failure. The cause for DCM is unknown (idiopathic, IDCM) with 20% estimated to be inherited. To identify the genetic defect for IDCM one must first map the chromosomal locus. Thus, we studied a four generation kindred with ten members having IDCM, detected by echocardiography. IDCM segregated as a highly penetrant autosomal dominant disorder. A genome search was performed using short tandem repeat polymorphic (STRP) markers. Two-point and multi-point linkage analysis was conducted *assuming penetrance to be 90%*. Approximately 90% of the genome was excluded by multi-point analysis of > 400 markers. Peak lod score of 5.78 was obtained at the marker DIS414 with θ = 0% recombination. Peak multi-point *lod score, also at D1S414*, was 6.37. Haplotype analysis identified recombination events between the disease gene and polymorphic markers in seven individuals. The region of 1q common to all ten affected individuals is flanked by *markers D1S249 and D1S549* which are approximately 20 cM apart. Reasonable candidates including myosin-binding protein-H, MEF-2D, renin and plasma membrane calcium transporting ATPase, are known to be localized to this region and studies are now underway using the positional candidate approach to isolate and identify the responsible gene. Identification of the genetic defect should elucidate the molecular basis for familial DCM, providing a means for precise diagnosis and screening of asymptomatic individuals at risk prior to the development of this disease, which is a necessary step in our ultimate goal of providing effective prevention and treatment of this disease.

2:15

408-2 A Functional Role for Endothelin-1 in Norepinephrine-Induced Ventricular Hypertrophy *in Vivo* and *in Vitro*

Samer Kaddoura. *MRCP, National Heart & Lung Institute, London, United Kingdom*

Background Endothelin-1 (ET-1) has potent effects upon cell growth. We tested the hypothesis that endogenous ET-1 plays a functional role in norepinephrine (NE)-induced ventricular hypertrophy by studying physical indices