133 HEMODYNAMIC AND LEFT VENTRICULAR VOLUME AND FUNCTION CHARACTERISTICS IN THALASSEMIA MAJOR (Thal)

Aaron R. Levin, Arthur A. Klein, Kathryn H. Ehlers, Joseph H. Graziano, Mary Allen Engle, The New York Hospital-Cornell Medical Center, Department of Pediatrics, New York City.

Hemodynamic and left ventricular (LV) volume and function characteristics obtained at cardiac catheterization were evaluated in 12 patients with Thal aged 11-28 years (mean 20.4 years) and compared to values in 17 normal subjects. At the time of study, hemoglobin was 10.9 ± 1.6 Gm%. Right atrial and ventricular (RV), and pulmonary artery and wedge pressures were normal. LV and aortic pressures and RV and LV dP/dt were normal. Oxygen consumption [220.7 ± 47.5 cc/min] and cardiac index (Qs) [4.9 ± 0.8 Lit/min/M^2] were normal. LV end-diastolic (EDV) and end-systolic (ESV) volumes were increased [138.4 ± 38.9%, $p < 0.01$; 183.1 ± 49.5%, $p < 0.001$ respectively]. Stroke volume, however, remained normal, as did forward flow and stroke work. Ejection fraction (EF) was significantly reduced [90.7 ± 7.1%, $p < 0.01$]. Myocardial contractility index, Mass and V_{CF} were not altered. Left atrial maximal volume (LAMV) was significantly increased [140.1 ± 23.8%, $p < 0.01$] but LAMV/LVEDV remained normal. Isometric exercise resulted in no significant change in hemodynamic parameters. Cardiac rate increased less than 18.7% [from 90.9 ± 20.0 to 107.5 ± 17.9 beats/min] and Qs did not rise significantly. LVESV increased with no EDV change resulting in a fall in EF and V_{CF}. We conclude that in Thal: (1) Surprisingly good ventricular function was maintained despite duration and severity of disease; (2) LV volume changes resulted from the anemic high output state; (3) although normal, LVEF was slightly but significantly reduced; (4) isometric exercise with marked fall in EF and V_{CF} suggested poor myocardial reserve.

134 PRE- AND POST-OPERATIVE RIGHT VENTRICULAR VOLUME & FUNCTION CHARACTERISTICS IN TETRALOGY OF FALLOT

Aaron R. Levin, Arthur A. Klein, Myles S. Schiller, Sheryl R. Levin, Mary Allen Engle, Kathryn H. Ehlers, The New York Hospital-Cornell Medical Center, Department of Pediatrics, New York City.

Right ventricular volume and function characteristics were evaluated in 25 pre-operative and 28 post-operative patients aged 10 days to 24 years. Pre-operative patients were grouped according to the pulmonary-to-systemic flow ratio (Qp/Qs) and post-operatively according to magnitude of right ventricular (RV) peak pressure (pr.) and residual pulmonary-to-RV pressure gradients (Δ PA-RV). Pre-operatively: cardiac index (CI) was highest and pulmonary index (PI) was lowest in those with smallest Qp/Qs; RV end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and ejection fraction (EF) were all mildly depressed but not significantly different in various Qp/Qs groups. RV myocardial contractility index (MCI) approached normal for a systemic ventricle. Stroke work (SW) was lowest in patients with palliative left-to-right shunts (LRS). Post-operatively: EDV and ESV were elevated but highest in patients with high residual RV pr. or large Δ PA-RV. SV was normal. EF was depressed in all groups, being lowest in those with highest RV pr. or Δ PA-RV. SW and MCI were normal in low RV pr. RV outflow aneurysms were identified in 3/10 patients in the low RV pr. group and in 12/16 with highest residual pr. The incidence of pulmonary regurgitation (PR) was similar in each group. We conclude that post-operatively in patients with tetralogy of Fallot: (1) significant RV dysfunction persists being worst in those with high residual RV pr. and Δ PA-RV; (2) dysfunction is related to the incidence of RV outflow aneurysm and PR; and (3) elevated ESV results from large aneurysms with small diastolic to systolic volume change.

135 INTRACARDIAC CONDUCTION INTERVALS IN THALASSEMIA MAJOR

Aaron R. Levin, Mary Allen Engle, Kathryn H. Ehlers, Denis R. Miller, Arthur A. Klein, The New York Hospital-Cornell Medical Center, Department of Pediatrics, New York City.

In the natural history of Thalassemia Major (Thal) with hemochromatosis, problems of conduction become increasingly prevalent. Intracardiac conduction intervals were measured during cardiac catheterization in 12 patients with Thal aged 11-28 years (mean 20.4 years) and compared to those of 13 normal individuals aged 14-17 years (mean 15.5 years). In Thal, hemoglobin values were 10.9 ± 1.6 Gm% at the time of study. Five of the Thal group were receiving digoxin for supraventricular arrhythmia and none were in heart failure. Normal subjects had: PH 92.2 ± 15.1 msec; AH 69.6 ± 16.5 msec; PA 23.2 ± 6.1 msec; HV 43.7 ± 6.4 msec. Significant differences were noted in Thal patjents in PH and AH intervals: PH 135.0 ± 30.0 msec ($p < 0.001$); AH 107.9 ± 27.1 msec ($p < 0.001$). The PA time [26.8 ± 9.5 msec] and HV interval [38.0 ± 5.7 msec] were similar to normal. There were no differences in any parameters between Thal patients receiving or not receiving digoxin, but those receiving digoxin had slightly longer intervals for PH and AH: PH 143.0 ± 21.1 msec vs 130.0 ± 35.6 msec ($p < 0.001$ vs $p < 0.02$ compared to normal) and AH 118.0 ± 16.8 msec vs 100.7 ± 31.8 msec ($p < 0.001$ vs $p < 0.01$ compared to normal). The subtle conduction delay through the AV nodal-to-His bundle area revealed by this study is the first clinical and electrophysiological documentation of deranged function and may be related to previous pathological studies showing deposits of iron in the AV nodal area in patients with hemochromatosis. Such delay may be the earliest manifestation of functional abnormality so common in adolescent and adult patients with Thalassemia Major.

136 ADMINISTRATION OF INDOMETHACIN TO THE PREGNANT EWE RESULTS IN CONSTRICTION OF THE FETAL DUCTUS ARTERIOSUS

Daniel L. Levin; Lawrence J. Mills; Michael Parkey; James Garriott (Spon. by David Fixler) Univ. of Texas, Dallas

Administration of prostaglandin synthetase inhibitors directly to the fetal sheep has been shown to cause constriction of the ductus arteriosus and pulmonary hypertension. Since these drugs are given to pregnant women we sought to determine if the same effect occurred in the fetus with administration of such an agent to the pregnant ewe. Pregnant ewes were operated upon at 123, 124 and 135 days gestation. Catheters were placed into the fetal pulmonary (PA) and carotid arteries (CA), the superior vena cava and amniotic cavity and the maternal inferior vena cava and aorta. Starting the first postoperative day one ewe was given indomethacin 0.5 mg/kg I.V., another 1.0 mg/kg I.V., and the other 1 mg/kg PO TID for 3 to 4 days. Initially PA and CA pressures were equal however PA pressures rose to 8, 6, and 9 mmHg greater than CA pressures by 1, 2, and 4 days respectively. Fetal blood was analyzed by spectrophotofluorometry for indomethacin and was positive for indomethacin although at very low levels. Administration of indomethacin to the pregnant ewe by either intravenous or oral routes probably crosses the placenta and causes constriction of the fetal ductus arteriosus. Direct vasoconstriction of the pulmonary vascular bed may also occur. This may have profound effects on the fetal systemic and pulmonary circulations which may be detrimental to the fetus and newborn.

Supported by AHA Grant-In-Aid 76-878.

137 STUDIES ON THE PATHOGENESIS OF CALCIFIC AORTIC VALVE DISEASE: THE ROLE OF THE CALCIUM BINDING AMINO ACID γ CARBOXYGLUTAMIC ACID.

Robert J. Levy, Jane B. Lian, Paul M. Gallop, Spon. by Alexander S. Nadas. Harvard Medical School, Children's Hospital Medical Center, Department of Cardiology and Orthopedic Research, Boston, Mass.

γ Carboxyglutamic acid (Gla) is a recently discovered calcium binding amino acid, which has been shown to be present in the vitamin K-dependent clotting factors and in a new bone protein, osteocalcin. In prothrombin Gla synthesis occurs in a post-translational and vitamin K dependent enzymatic carboxylation of specific glutamic acid (Glu) residues. This reaction is inhibited by Dicumarol and other vitamin K antagonists with a net effect on clotting of anticoagulation. Furthermore, Gla has been shown to be present in metastatic and dystrophic calcifications, occurring in calcified atherosclerotic plaque, kidney stones, and subcutaneous nodules in dermatomyositis and scleroderma. The purpose of the present study was to determine if Gla is present in calcified aortic valve tissue from patients with congenital aortic stenosis and in cases of calcified aortic valve homografts and xenografts. Pathologic aortic valve tissue was obtained at cardiac surgery from 5 patients. Normal aortic valves were obtained from 2 patients at autopsy, and the Truncal valve from a patient with a calcified aortic valve homograft was also studied. Valve specimens were rinsed with saline and dried. One calcified aortic valve was extracted with .5M EDTA (pH8). The tissue and the EDTA extract were next subjected to 2N KOH hydrolysis, Dowex-1 chromotography, and automated amino acid quantitation of Gla. Gla was detected in all calcified aortic valve tissues. No Gla was found in the normal aortic valve tissue or in the Truncal valve. We conclude that the specific calcium binding amino acid, Gla, may be linked to the pathologic calcification of aortic valves. If Gla containing proteins can be related to the pathogenesis of calcific aortic valve disease, then vitamin K antagonism with Dicumarol or related compounds might retard the calcification process.

138 PULMONARY VASCULAR RESPONSES IN UNSEDATED NEWBORN LAMBS.

James E. Lock, Flavio Coceani, Peter M. Olley (Spon. by Richard D. Rowe). The Hospital for Sick Children, Department of Pediatrics, Toronto.

Pulmonary vascular responses to histamine (H) and acetylcholine (A) were studied in 5 unsedated newborn lambs (3-5 wks, 5-9 kg). Flow probes were placed around the right and left pulmonary arteries (RPA, LPA); 5-7 days were allowed for full recovery (respirations < 36, clear lungs on X-ray). Catheters were then placed in the aortic root (Ao) and either R or LPA. The maximum PA gradient across a probe was 3 mmHg. Bolus injections of H (2-10μg) and A (2-10μg) were made into R or LPA and, as a control, into Ao. RPA flow, LPA flow, Ao and PA pressures were measured continuously. The fraction of total cardiac output directed to the injected lung (Q_{inj}/Q_T), systemic and pulmonary vascular resistances (SVR, PVR) were calculated before, and 10, 20, 30, and 60" after injections.

A into Ao reduced SVR (44%)* and PVR (18%)*, but there was no change in Q_{inj}/Q_T (51 vs 52%). Injection of A into RPA or LPA yielded the same results: SVR fell 49%*, PVR fell 17%*, but again, no change in Q_{inj}/Q_T (49 vs 52%). H into Ao also decreased SVR (34%)* and PVR (22%)* without changing Q_{inj}/Q_T. However, H into RPA or LPA decreased Q_{inj}/Q_T in all 6 experiments (62 vs 47%).*

In this experimental model, each lung "sees" the same neural input, as well as left atrial, intrathoracic, and PA pressures. Thus, one lung serves as a control for the other, allowing study under more physiologic conditions. The results indicate that, in newborn lambs, A has minimal direct effects on the lungs, and causes pulmonary "vasodilation" via its effect on the systemic circuit. In contrast, H is a direct pulmonary constrictor. *$p \leq 0.02$