901-107 Fetal Model of Single Ventricle Physiology: Hemodynamic Effects of Epinephrine, Sodium Bicarbonate, and Calcium Chloride

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Neonatal and infant patients (pts) with single ventricle physiology (SVP) following bypass, for e.g. pts after stage I repair of hypoplastic left heart syndrome (HLHS), often suffer from hemodynamic instability early after surgery. Specific hemodynamic effects of pharmacologic resuscitation are poorly understood. To examine these issues a model of SVP was created in fetal lambs: a Damus procedure was performed in fetal lambs using a 10 mm ePTFE tube graft and the main pulmonary artery was ligated distally. Pulmonary blood flow (PBF) was provided by creating a 6 mm systemic to pulmonary artery shunt. Neonatal lambs with SVP were delivered normally at term. At 48 hours after birth the lambs (n = 10) were instrumented and monitored. Ultrasonic flow probes were placed on the aorta and the shunt to measure systemic blood flow (SBF) and PBF. Interventions were performed in random order before and after cardiopulmonary bypass and a 30 min period of hypothermic circulatory arrest to mimic the clinical setting e.g. stage I repair of HLHS. The effects on systemic and pulmonary vascular resistances (SVR and PVR), PBF, and SBF are shown below

Intervention	PBF	SBF	PVR:SVR	PBF[1]	SBF[1]	PVR:SVR[1]
Epi infusion[2]	13.5*	20.8*	+6.8	13.8*	14.5*	−7.5
Bicarbonate[3]	9.2*	13.5*	−4.5	10.2*	16.6*	−0.4
Ca chloride[4]	7.9*	16.8*	+2.6	12.64*	18.7*	−1.7
Epi bolus[5]				94.1*	−68.8*	−88.8*

*Values represent percent increase or decrease from baseline. 1: post bypass; 2: epinephrine 0.1 μg/kg/min; 3: sodium bicarbonate 2 mEq/kg 4: calcium chloride 10 mg/kg; 5: epinephrine 1 in 10,000: 0.05 ml/kg, * P < 0.05.*

In summary this is the first reported model which provides a useful tool to study neonatal SVP. Epinephrine infusion, sodium bicarbonate bolus, and calcium chloride bolus increased both PBF and SBF. Epinephrine bolus even at half the recommended code dose caused a tremendous increase in PBF and severe decrease in systemic blood flow causing metabolic acidosis. On average it took 5 min for the flows to return to base line values. This suggests that epinephrine boluses should be used judiciously and probably be considerably smaller in the management of patients with SVP. Calcium chloride had a good inotropic effect without significant effect on PVR:SVR ratio.

PERIPHERAL VASCULAR DISEASE/THROMBOSIS/EMBOLISM — CLINICAL

901-108 Atheromatous Disease of the Thoracic Aorta: A Transesophageal Echocardiography and Autopsy Correlative Study

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Transesophageal echocardiography (TEE) is widely used for the evaluation of thoracic aortic pathology, most recently atheromatous disease. Unfortunately, there have not been any studies correlating TEE and autopsy findings of atheroma to validate this use of the technique. Also, the TEE grading systems for aortic atheromatous disease currently in use have not been established to parallel pathologic grading systems, nor has their clinical significance been tested.

We retrospectively evaluated all patients who underwent TEE at our institution between 1988 and 1993 and subsequently underwent autopsy within 30 days of the TEE study. We identified 13 patients with adequate thoracic aortic tissue available for pathologic analysis who also had a complete TEE examination of either the ascending, arch or descending thoracic aortic segments. Among these there were 21 complete tissue segments available which had been adequately imaged. All segments were reviewed and compared with respect to: (1) surface area and pattern of atheroma, (2) area and pattern of calcification, (3) depth of mural ulceration, and (4) type and description of mural thrombus; also (5) measurements of maximum wall thickness, (6) sizing of any aneurysm, and (7) characterization of any dissection.

Significant correlations were found using this detailed grading system for surface area of atheroma (kappa test, $\kappa = 0.29 \pm 0.26$), wall thickness (correlation, r = 0.56), correct identification of the one ascending aortic aneurysm, and absence of dissection or mural thrombus. The correlations for pattern of atheroma, area and pattern of calcification and depth of ulceration did not reach statistical significance. However, there was an 86 to 100% agreement for these lesion characteristics when allowing for 1 category of variation.

Conclusions: There is a good correlation between TEE and autopsy findings with respect to: (1) atheroma surface area, (2) aortic wall thickness, and (3) the identification of aortic aneurysm. TEE and autopsy grading of lesion characteristics have excellent agreement when allowing for one category of variation. The clinical relevance of this grading system requires further study.

901-109 Value of Visualizing Atherosclerotic Plaques on the Thoracic Aorta by Transesophageal Echocardiography in Conjunction with Pharmacologic Stress

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Detection of atherosclerotic plaques within the thoracic aorta (TA) by transesophageal echocardiography (TEE) has been shown to be a useful marker to detect coronary artery disease (CAD). Dobutamine (Dob) stress echocardiography can induce segmental wall motion abnormalities (SWMA) in the presence of CAD. To determine the value of visualizing atherosclerotic plaques on the TA in conjunction with Dob-TEE, 60 pts (54 males, 6 females; mean age 59 ± 13 yrs) with chest pain syndrome were studied. All pts underwent coronary angiography. Dob was infused in 3-min increments from 5 to 40 mcg/kg/min. Dob-TEE was considered positive if new or worsening of previously present SWMA were noted. Atherosclerotic plaques visualized on TA were divided into simple and complex lesions. Simple lesions were defined as intimal thickening or luminal irregularities, and complex lesions were protruding, ulcerated or mobile plaques noted. *Results:* Significant CAD (≥50% stenosis) was present in 49 pts and 11 pts had normal or non-significant disease. Sensitivity (SE), specificity (SP), positive (+PV), negative (−PV) predictive values, and diagnostic accuracy (DA) are:

	SE	SP	+PV	−PV	DA
Dob-TEE	94%	73%	94%	73%	90%
TA-TEE	90%	80%	93%	73%	88%

The TA showed atherosclerotic plaques in 45 of 49 pts with positive Dob-TEE and it was free of disease in 9 of 11 pts with negative Dob-TEE (90% agreement). The presence of complex lesions was significantly higher in pts with multivessel disease (MVD) (21 of 32 pts 66%) than in those with single vessel disease (SVD) (3 of 17 pts 18%), $p < 0.01$. While simple lesions were more common in SVD (11 of 17 pts 65%) than in MVD (9 of 32 pts 28%), $p < 0.01$. *In conclusion,* TA-TEE and Dob-TEE highly concur in detecting CAD. Visualization of complex lesions on TA-TEE *before* Dob-TEE should alert for the possibility of MVD.

901-110 Three-Dimensional Ultrasound Can Accurately Reconstruct Intravascular Thrombi: In Vitro Validation

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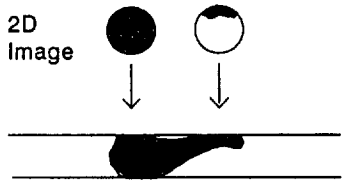
High-frequency ultrasound can potentially display gross morphologic changes during thrombus formation and lysis. Current intravascular ultrasound (IVUS) devices, however, provide only 2-dimensional cross-sectional images with limited overall appreciation of thrombus size and 3-dimensional (3D) configuration. The purpose of this study was to explore the ability of 3D reconstruction of serial ultrasound images to provide a quantitative assessment of intravascular thrombi. We therefore imaged 11 arterial thrombi of varying shape and volume (10 to 116 mm^3). To avoid thrombus disruption, we used an epivascular approach (also suitable for transvenous imaging) with a 20 MHz IVUS catheter withdrawn at 1 mm/sec. A 3D voxel image intensity data set was reconstructed, and thrombus volume was semiautomatically extracted based on its intensity. Calculated volume was compared with directly measured values by volume displacement in a miniature cylinder.



Longitudinal section of 3D reconstruction

Results: 3D reconstruction provided previously unobtainable longitudinal and 3D views that improved spatial appreciation of thrombus size, shape and channel formation. Calculated thrombus volumes agreed well with actual volumes: $y = 0.92x + 2.4$, r = 0.98, SEE = 5 mm^3, mean error = 1 ± 5 mm^3

(ns vs 0). *Conclusion:* 3D reconstruction can improve spatial appreciation of the shape of thrombi and accurately measure their volumes. This approach, suitable for epivascular or transvenous imaging, could potentially be used to study thrombus formation and lysis in research and clinical studies.

PHARMACOLOGY — BASIC

901-111 ACE Inhibition (Quinapril) Modulates Central Vasopressin in the Rat

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The beneficial effects of ACE inhibitors (ACEI) in heart failure and hypertension appear to be mediated not only by their influence on circulating ACE or tissue ACE in the heart. Previous studies have also implicated the brain as a possible site of actions for ACEI, e.g. by modifying central cardiovascular mechanisms. Their effects on central vasopressin (AVP), which is an important neurotransmitter in central cardiovascular regulation, are not known.

Following chronic administration of Quinapril (6 mg/kgBW; 6 weeks, p.o.) ACE activity (in vitro autoradiography using a specific ACE inhibitor [^{125}I]351A) was markedly inhibited in the thalamus (38%), hypothalamus (37%), hypophysis (35%), cerebellum (36%) and plexus choroideus (20%) suggesting Quinapril may cross the blood brain barrier after chronic treatment. To study the influence of ACEI on central vasopressin, we determined the AVP content of 19 microdissected brain areas in rats treated with Quinapril. Regarding the hypothalamic AVP-producing nuclei, increased AVP levels could only been demonstrated in the paraventricular (PVN; Quinapril: 292 ± 197 vs. 2209 ± 568 pg/mg protein of controls; $p < 0.001$), but not in the supraoptic (SON) and the suprachiasmatic nucleus (SCN). Interestingly, vasopressin synthesizing cells in the PVN project not only to the posterior pituitary (like SON), but also to the lower brain stem and the spinal cord suggesting an important role of the PVN in the regulation of the cardiovascular system. Also, AVP content was sign. reduced in the median eminence (15643 ± 9240 vs. 28321 ± 4969, $p < 0.001$), where the hormone is mainly concentrated in the hypothalamo-hypophysial tract. Furthermore, sign. changes were registered in the central amygdala, in the subcommissural organ and dorsal raphe nucleus.

Conclusions: Autoradiographic study in vitro indicates that after chronic treatment Quinapril is able to cross the blood brain barrier and suppress central ACE activity. ACE inhibition with Quinapril markedly influences vasopressin in important brain areas which are involved in central cardiovascular regulation. Therefore, central modulatory effects of ACE inhibitor may contribute to their overall therapeutic efficacy.

901-112 Attenuation of Myocardial Stunning by a Novel Nonglucocorticoid 21-Aminosteroid Inhibitor of Lipid Peroxidation

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Lipid peroxidation induced by oxygen free radicals has been implicated in myocardial dysfunction during reperfusion. The effect of a new 21-aminosteroid (Lazaroid, U74389G) that inhibits lipid peroxidation was studied in isolated, isovolumic rat hearts subjected to 20 min of normothermic ischemia and subsequent repefusion for 30 min. Male Sprague-Dawley rats (350–400 g) were randomized into three groups. Group 1 (Control; n = 13) received vehicle before sacrifice and drug-free reperfusion, group 2 (Pretreatment; n = 11) received 6 mg/kg (iv) U74389G 30 min prior to sacrifice, and group 3 (Reperfusion; n = 11) received 5 μM U74389G in the reperfusion solution. LV developed pressure (LVDP) and end-diastolic pressure (LVEDP) were measured; maximum +dP/dt and the time constant of relaxation, Tau (τ), were calculated.

	LVDP (mmHg)	+dP/dt (mmHg/sec)	LVEDP (mmHg)	Tau (msec)
Control group				
Baseline	127 ± 6	2892 ± 127	5 ± 1	23 ± 1
30 min reperfusion	66 ± 5	1673 ± 140	30 ± 6	58 ± 9
Pretreatment group				
Baseline	122 ± 3	2893 ± 97	7 ± 1	24 ± 1
30 min reperfusion	112 ± 3**	3171 ± 159**	14 ± 3*	28 ± 3*
Reperfusion group				
Baseline	124 ± 4	2744 ± 77	5 ± 1	21 ± 1
30 min reperfusion	108 ± 5**	2785 ± 129**	14 ± 5*	32 ± 9*

*$P < 0.05$ vs. Control group, 30 min reperfusion; **$P < 0.01$ vs. Control group, 30 min reperfusion

Conclusion: Whether administered before ischemia or during reperfusion in this model, U74389G attenuates the systolic and diastolic dysfunction of myocardial stunning, most likely by protecting the lipid component of cell membranes from peroxidation by oxygen-derived metabolites.

901-113 Endothelin Receptor Antagonists in a Beagle Model of Pulmonary Hypertension: Contribution to Possible Potential Therapy?

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The idealvasodilator for pulmonary hypertension (PH) would decrease pulmonary arterial pressure with minimal systemic hypotension. The present study was undertaken to investigate the pharmacologic effect of endothelin receptor antagonists on cardiopulmonary hemodynamics in an animal model of PH. We recently developed a beagle model of PH which allows accurate determination of cardiopulmonary hemodynamics and which is associated with elevated plasma endothelin-1 concentrations similar to PH in humans. Twelve beagles (PH, n = 6; and Control, n = 6) were studied during baseline conditions and during right atrial infusion of FR139317 (the ETA receptor antagonist), RES-701-1 (the ETB receptor antagonist), nitroglycerin, and prostaglandin E1. PH was induced in experimental animals 8 weeks after an injection of 3 mg/kg dehydromonocrotaline. The table showed hemodynamic values of PH beagles at baseline and during drug infusion. FR139317 lowered pulmonary and systemic arterial pressure both in pulmonary hypertensive and control animals, with a significantly greater effect on pulmonary arterial pressure in pulmonary hypertensive animals. RES-701-1 increased pulmonary arterial pressure only in PH. Nitroglycerin depressed pulmonary and systemic arterial tone equally well in controls and animals with PH. Prostaglandin E1 produced a greater decrease in systemic arterial pressure in pulmonary hypertensive than in normal animals, despite same effect on pulmonary arterial pressure in both.

	Baseline	FR139317 200 μg/kg/min	RES-701-1 100 μg/kg/min	Nitroglycerin 10 μg/kg/min	Plastaglandin E1 0.4 μg/kg/min
MSAP (mmHg)	106 ± 5	101 ± 7	109 ± 6	87 ± 6*	93 ± 7*
MPAP (mmHg)	33.2 ± 5.9	26.8 ± 3.7*	36.2 ± 6.4	27.0 ± 5.1*	27.8 ± 4.1*
SVR (dynes/s/cm^5)	4685 ± 439	4581 ± 608	4771 ± 597	3767 ± 229*	3718 ± 120*
PVR (dynes/s/cm^5)	1237 ± 441	867 ± 164*	1319 ± 299	856 ± 207*	870 ± 243*

* Significant difference between baseline and drug infusions at $P < 0.05$ levels. MSAP: mean systemic arterial pressure, MPAP: mean pulmonary arterial pressure, SVR: systemic vascular resistance, PVR: pulmonary vascular resistance

Conclusions: ETA receptor antagonists decrease pulmonary arterial pressure in a beagle model and therefore may be clinically useful for therapy of pulmonary hypertension.

PHARMACOLOGY — CLINICAL

901-114 Women Have a Higher Response Rate than Men to the Antihypertensive Calcium Channel Blocker Amlodipine

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There is a lack of data on gender difference in response to the newer antihypertensive medicines. The Amlodipine Cardiovascular Community Trial was designed to determine the blood pressure (BP) response of patient subgroups with mild-moderate hypertension to amlodipine besylate monotherapy (5–10 mg/day). After a 2 week placebo phase, patients received amlodipine for a 4 week efficacy/titration phase followed by a 12 week maintenance phase. Goal BP was defined as a decrease in diastolic BP by 10 mmHg or more *plus* a diastolic BP of less than 90 mmHg. Baseline systolic BP in mmHg was 153 ± 16 and 155 ± 16 and diastolic BP 101 ± 4 and 100 ± 4 for males (n = 702) and females (n = 382), respectively. Decreases in BP at 4 weeks were greater in females than males for both systolic (−19 vs −15 mmHg, $p < 0.0001$) and diastolic BP (−14 vs −12 mmHg, $p < 0.0001$). Results were maintained at 12 weeks. Ninety-one percent of females achieved goal BP compared to 83% of men ($p = 0.001$). The greater response to amlodipine by women remained significant after adjusting for: age, weight, dose (mg/kg), baseline BP, and drug compliance (99% in both women and men). There was no difference in decrease in systolic and diastolic BP for women on hormone replacement (−18 and −14 mmHg) versus those not on hormone replacement (−19 and −14 mmHg). Thus, hormone replacement in women did not account for the gender difference in BP response. Women reported edema