

Investigation of the role of α_2 -adrenoceptors in contractile responses of the isolated bovine tail artery and vein. M IOUDINA and DC DYER, Dept. Biomedical Sciences, Iowa State University, Ames, IA, 50011. The purpose of this study was to determine the role of α_2 -adrenoceptors in contractile responses in bovine tail artery (BTA) and vein (BTV). Endothelium -denuded BTA and BTV rings were placed in 10ml isolated tissue baths containing a modified Krebs' solution at 38.5°C and aerated with O₂/CO₂ (95:5). Isometric contractions were monitored by a MacLab system connected to a computer. The ring segments were initially stretched to a tension of 15g (artery) and 4g (vein) and then allowed to equilibrate over a 60-min period. Contractile responses to 120mM KCl were obtained after the equilibration period and this was set as the 100% response. Failure to relax to 1 μ M acetylcholine was used to confirm endothelium removal. After a one-hour incubation period with antagonists, UK 14,304, an α_2 -adrenoceptor agonist, was added cumulatively to the tissue baths in order to obtain concentration response relationships. Tissues without antagonist were used as a control. UK 14,304 caused concentration dependent contractions in BTV and developed 3.3 \pm 0.3g maximum tension or 62.8 \pm 5.2% (n=9) of that to 120mM KCl. Antagonist potencies (pK_B) were calculated based on EC₂₅ contractile response to UK 14,304 and were 7.95 \pm 0.34 for idazoxan (n=7), 6.42 \pm 0.21 for ARC 239 (n=4) and 7.44 \pm 0.46 for prazosin (n=4). The maximum contraction to UK 14,304 in BTA was only 6 \pm 1.1 % (n=4) of that to 120mM KCl. Our findings suggest that (α_2 -adrenoceptor agonists caused concentration dependent contraction in BTV. The high potency (pK_B) for idazoxan and prazosin against UK 14,304 are taken as evidence for the presence of α_{2B} and/or α_{2B} but less likely α_{2A} -adrenoceptor subtypes in BTV. However, α_2 -adrenoceptor subtype identification needs further investigation. It does not appear that α_2 -adrenoceptors play a significant role in vasoconstriction of the BTA. Supported in part by USDA formula funds.

VEGF and VEGF Receptor Expression in Human Hearts. RJ TORRY, J SCHWARTZ, D HSU, SJ MILLER, CA LABARRERE, DS TORRY. College of Pharmacy and Health Sciences, Drake University, Des Moines, IA; Experimental Pathology, Methodist Research Institute, Indianapolis, IN; and Univ. of Tennessee School of Medicine, Knoxville, TN. Vascular endothelial growth factor (VEGF) is thought to be an important regulator of coronary angiogenesis during hypoxia. We have previously shown a significant temporal relationship between microvascular fibrin deposition, VEGF immunoreactivity, and capillary phenotypic changes in biopsies of transplanted human hearts. However, the relative changes in endogenous VEGF or VEGF receptor (flt-1, flt-4, KDR) expression in human hearts is not known. Utilizing quantitative RT-PCR, heart biopsies with significant microvascular fibrin deposits (n = 5) expressed ~3-fold more VEGF mRNA than biopsies without fibrin deposits (n = 5; p = 0.02). Serum VEGF titers were also significantly greater (p=0.01) in recipients with microvascular fibrin deposits (372.9 \pm 66.7 pg/ml; n=1 8) compared to recipients without fibrin (172.1 \pm 25.0 pg/ml; n=16). Preliminary VEGF receptor expression data from pooled donor hearts suggest human myocardium expresses predominately flt-1, lesser flt-4, and little/no KDR mRNA. In conclusion, increased VEGF production following microvascular fibrin deposition in transplanted human hearts combined with prominent expression of VEGF receptors support the hypothesis that VEGF may act in a paracrine manner to promote microvascular phenotypic changes associated with graft survival in human myocardium.

Paradoxical dual effects of lidocaine on carotid occlusion reflex in mice. W SUN and MW CHAPLEAU. Dept. of Int. Med., Univ. of Iowa and Vet. Aff. Med. Ctr., Iowa City, IA 52242. Carotid sinus (CS) chemo- and baroreceptors are important regulators of blood pressure (BP). Our overall goal is to define sensory mechanisms of these receptors using genetically-manipulated mice. Bilateral carotid artery occlusion (BCO) reduces baroreceptor activity and may increase chemoreceptor activity. The aim of this study was to determine effects of the Na⁺ channel blocker lidocaine topically applied to CS on the BCO reflex in anesthetized mice. The mice were ventilated and the vagus and aortic depressor nerves sectioned. BCO decreased mean CS pressure from 64 \pm 3 to 14 \pm 2 mmHg and reflexly increased systemic BP from 63 \pm 3 to 98 \pm 7 mmHg (n=8, P<0.05). CS lidocaine had minimal effect on baseline BP, paradoxically enhanced the BCO reflex at low doses (n=6), and attenuated the reflex with longer exposure to high doses (n=4, see table, *P<0.05).

	Control	Lidocaine 0.2-0.5%	Lidocaine 1-2%	Recovery
Baseline BP (mmHg)	63 \pm 3	67 \pm 4	59 \pm 9	62 \pm 3
BCO Reflex (Δ mmHg)	+36 \pm 5	+51 \pm 9*	+9 \pm 5*	+38 \pm 4

The impaired BCO reflex during high-dose lidocaine is consistent with expected blockade of Na⁺ channels. The enhanced BCO reflex at low doses suggests a novel excitatory effect of lidocaine on baro- or chemoreceptors. Furthermore, the large effects of lidocaine on the BCO reflex despite little effect on baseline BP suggest differences in the mechanisms of dynamic vs. tonic CS reflex control of BP.

Angiotensin selectively activates a subpopulation of post-ganglionic sympathetic neurons in mice. XY MA, K BIELEFELDT, FM ABBOD, and MW CHAPLEAU. Department of Internal Medicine, University of Iowa and Veterans. Aff. Med. Ctr., Iowa City, IA, 52242. We have recently demonstrated that intravenous angiotensin II (A-II) increases renal sympathetic nerve activity in mice before and after ganglionic blockade with hexamethonium. The present study tested the hypothesis that A-II directly activates a subpopulation of post-ganglionic sympathetic neurons. Neurons were dissociated from aortic-renal and celiac ganglia of C57/BL6J mice. Cytosolic calcium concentration ([Ca²⁺]_i) was measured using fura-2. Addition of A-II to the bath solution (200nM) increased [Ca²⁺]_i by 54 \pm 6 % in 14 of 21 neurons tested (p<0.01). The remaining 7 neurons failed to respond to A-II, but showed a calcium increase after KCl-induced depolarization. The A-II-induced increase in [Ca²⁺]_i was dose-dependent, desensitized, and was abolished by removal of extracellular Ca²⁺ (n=21). To test the effect of A-II on calcium influx, intracellular Ca²⁺ stores were depleted with thapsigargin in the absence of extracellular Ca²⁺. Changing the bath to calcium-containing solution led to a [Ca²⁺]_i rise which further increased after A-II. We conclude that 1) A-II selectively increases [Ca²⁺]_i in a subpopulation of post-ganglionic renal sympathetic

neurons, and 2) Ca^{2+} influx contributes importantly to the rise in $[Ca^{2+}]_i$. The results are in agreement with our previous finding of an A-II-induced increase in renal sympathetic nerve activity in intact mice. We speculate that selective activation of this particular subpopulation of sympathetic neurons may exert unique actions on renal function.

Total body bone mineral density, bone mineral content and N-telopeptides in prepubertal children with cerebral palsy. TD CROWE, AR BAUER, MJ OAKLAND, and TS KENNEDY. Iowa State University, 2312 Food Sciences Building, Ames IA, 50011. Children with cerebral palsy (CP) often have increased risk of bone fractures compared with healthy children, presumably due to low bone mineral density (BMD), bone mineral content (BMC), decreased weight-bearing physical activity, inadequate calcium intake, and the use of anticonvulsant medication. Although several studies have used dual-energy X-ray absorptiometry (DXA) to determine BMD and BMC in children with CP, concurrent measurements of biochemical markers of bone demineralization have not been reported. We used DXA to measure total body BMD and BMC in 6-12 year old, prepubertal, white children with spastic-type CP (n=11; 6 females, 5 males). Urinary cross-linked N-telopeptides of type I collagen (NTX) was also measured as an indicator of bone resorption. Z-scores were calculated based on age and sex-matched published reference values. Z-scores were <-2.0 in 8 of 11 children for BMD, and 10 of 11 children for BMC. Urinary NTX was increased (Z-score +6.6) in children with CP, denoting the breakdown of mature cross-linking in bone collagen. These results indicate that children with CP have an imbalance between bone formation and degradation. Because failure to attain optimal bone mass during childhood and adolescence increases later risk of osteoporosis and fractures, early intervention strategies are necessary to improve bone status in children with CP.

Monitoring intraluminal PCO_2 : a comparison of air-flow and fiber optic methods. P WALL, L HENDERSON, C BUISING, T RICKERS, A CÁRDENAS, T MATTSON, A LARKIN, L WITTKOPF, D DAVIS, IF RAYMOND, L OWENS, D MOORMAN, G TIMBERLAKE. Surg Ed & Trauma, IA Methodist Med Ctr, Des Moines, IA 50309 and Drake University, Des Moines, IA 50311. The clinical use of gastrointestinal intraluminal PCO_2 ($GI P_iCO_2$) information is increasing. Therefore, determining the potential caveats of different $GI P_iCO_2$ monitoring systems is clinically important. Methods: Air-flow (Tonocap®) and fiber optic (Neotrend®) PCO_2 monitoring systems were used to measure the PCO_2 of humidified air containing 5 and 10% CO_2 . The same systems were also used simultaneously to monitor the gastric P_iCO_2 of 15 dogs during hemorrhage (mean arterial pressure 40-45mmHg for 30 min, then 30-35mmHg for 30 min) and three resuscitation protocols. Results: The systems agreed *in vitro*. The fiber optic system, however, provided higher and more rapidly changing gastric P_iCO_2 values with hemorrhage than did the air-flow system: 69.7 ± 5.0 & 58.6 ± 4.5 mmHg at baseline and 145.8 ± 11.7 & 84.5 ± 6.4 mmHg (mean \pm SEM, $p < 0.05$) at end hemorrhage, respectively. Conclusions: Despite *in vitro* agreement, the use of air-flow based methods for determining $GI P_iCO_2$ may influence the values obtained. Non-sample removing techniques, such as fiber optic methods, for monitoring $GI P_iCO_2$ are preferable because they neither deliver O_2 to nor remove CO_2 from the local microenvironment. (Support: Drake U, Pfizer, VA Central IA Health Care Sys, DM Research & Ed Corp, Arrow Int'l, Diametrics)

Fiber optic P_iCO_2 at four gastrointestinal sites during hemorrhage and resuscitation. L OWENS, P WALL, T RICKERS, L HENDERSON, C BUISING, A CÁRDENAS, F RAYMOND, B FREEMAN, M WIATER, JM LANGLEY, R VINCENT, D MOORMAN, G TIMBERLAKE. Surg Ed & Trauma, IA Methodist Med Ctr, Des Moines, IA 50309 and Drake University, Des Moines, IA 50311. As clinical gastrointestinal P_iCO_2 monitoring increases, the equivalence of different GI sites for monitoring patient status becomes important. Methods: In two hemorrhage (H) and resuscitation (R) studies, fiber optic (Neotrend®) PCO_2 monitoring systems were used simultaneously to measure P_iCO_2 in the esophagus, stomach, and duodenum (5 mongrel dogs, 1st study) and in the stomach, duodenum, and ileum (10 mongrel dogs, 2nd study). Results: During H, P_iCO_2 increased at all sites in all dogs, but the magnitude of the increases varied. No site was consistently the highest. During R, significant differences between each of the sites (including direction of change) existed in 3 of the 4 surviving dogs (1st study, $p \leq 0.037$) and 7 of the 8 surviving dogs (2nd study, $p < 0.05$). The other 2 dogs approached significance ($p = 0.057$ 1st study and $p = 0.081$ 2nd study). During R duodenal P_iCO_2 levels were topped out in 5 of the 8 surviving dogs (2nd study). Conclusions: Various sites $GI P_iCO_2$ monitoring sites may be acceptable for aiding initial severity of shock assessment. But, the energy status in a specific GI site during resuscitation cannot be assumed to indicate the energy status of any other GI site. (Support: Pfizer, VA Central [A Health Care Sys, DM Research & Ed Corp, IA Space Grant Consortium, Diametrics)

Effect of enalaprilat on gastrointestinal intraluminal PCO_2 during hypotensive resuscitation. T RICKERS, P WALL, L HENDERSON, C BUISING, A CÁRDENAS, F RAYMOND, D HOGANSON, C BRUNKAN, J GALE, JM LANGLEY, L OWENS, D MOORMAN, G TIMBERLAKE. Surg Ed & Trauma, IA Methodist Med Ctr, Des Moines, IA 50309 and Drake University, Des Moines, IA 50311. Enalaprilat may improve GI mucosal energy status (decrease P_iCO_2) by increasing splanchnic perfusion. Methods: Dogs were anesthetized, instrumented (fiber optic P_iCO_2 probes), bled (MAP=40-45mmHg, 30min then 30-35mmHg, 30min), resuscitated (LRS IV ≤ 60 ml/kg/hr, MAP=40-45mmHg, 150min). A constant rate infusion (CRI) of enalaprilat (0.02mg/kg/hr, n=5) or saline (n=5) started 30min into resuscitation. Results: 4 survived hemorrhage in each group. (Averages \pm SEM)

	Start CRI P_iCO_2 (mmHg)			End Resus. P_iCO_2 (mmHg)		
	Gastric	Duod	Ileal	Gastric	Duod	Ileal
Enal.	178 \pm 17	199 \pm 0	189 \pm 10	153 \pm 33	199 \pm 0	185 \pm 21
Saline	113 \pm 31	177 \pm 221	109 \pm 31	126 \pm 31	146 \pm 52	97 \pm 31

Conclusions: No significant decrease in P_iCO_2 at any site occurred with enalaprilat as compared to saline. The fiber optic probe topped

out at 199mmHg in the duodenum of all enalaprilat dogs vs one saline (n=1); the stomach (n=2) vs (n=1); and the ileum (n=2) vs (n=0). Given more time, differences may have developed between the groups. (Support: Pfizer, VA Central IA Health Care Sys, DM Research & Ed Corp, IA Space Grant Consortium, Diametrics, Arrow Int'l)

Pre-hemorrhage Gatorade® effects on GI P_iCO_2 . T MATTSON, P WALL, M MCBRIDE, D DAVIS, A CÁRDENAS, A KIN, L WITTKOPF, F RAYMOND, D MOORMAN, G TIMBERLAKE. Surg Ed & Trauma, IA Methodist Med Ctr, Des Moines, IA 50309. We hypothesized that provision of a glucose/electrolyte solution (Gatorade®) rather than fasting pre-bleed might be beneficial for maintaining GI mucosal energy status (theoretically inversely related to GI P_iCO_2) during hemorrhage (H). Methods: After 18hr with only water (W), Gatorade® (G), or chow and water (C), rats were anesthetized; instrumented (gastric & colonic fiber optic probes); hemorrhaged (MAP= 35-40mmHg >60min until MAP<30mmHg for >10min or <25mmHg for >1 min, or 120min elapsed); resuscitated (R) for 3hr with lactated Ringers (60ml/hr as needed for MAP=75-80mmHg); then euthanized. Results: Mean±SE (mmHg), g=gastric c=colonic, i=intraluminal.

	start H	start R	1hrR	2hr R	3hr R
W g P_iCO_2	89±18	78±15	86±99	65±7	54±14
W c P_iCO_2	68±5	76±3	58±6	51±2	50±2
G g P_iCO_2	102±18	156±25	132±21	110±17	93±19
G c P_iCO_2	64±2	74±8	59±3	57±3	50±3
C g P_iCO_2	106±12	113±13	82±6	82±12	81±11
C c P_iCO_2	77±7	106±7	68±4	64±4	66±10

6 of 12 W, 7 of 12 G, and 13 of 15 C rats survived to euthanasia. Conclusions: Gastric P_iCO_2 was highest and underwent the greatest change in the Gatorade® rats (p<0.05). Colonic P_iCO_2 was similar in the Gatorade® and fasted rats and higher in the chow rats (p<0.05). Gatorade® may have exacerbated the effect of hemorrhage on gastric mucosal energy status. Why this occurred requires further investigation. (Support: Pfizer, VA Central IA Health Care Sys, Drake U, Diametrics)

The effect of enalaprilat on portal vein and superior mesenteric artery flow. A CÁRDENAS, P WALL, L HENDERSON, C BUISING, T RICKERS, F RAYMOND, R VINCENT, S BELL, K DANIELS, L OWENS, A CHENDRAHSEHKAR, D MOORMAN, G TIMBERLAKE. Surg Ed & Trauma, IA Methodist Med Ctr, Des Moines, IA 50309 and Drake University, Des Moines, IA 50311. Enalaprilat administration during resuscitation may be useful for improving splanchnic blood flow. Methods: Ten mongrel dogs were anesthetized, instrumented, and bled (MAP of 40-45mmHg, and then 3035mmHg for periods of 30min). The dogs were then resuscitated to MAP 40-45mmHg for 30min. At this point 5 of the dogs were given a constant rate infusion (CRI) of enalaprilat (0.02mg/kg/h), and the other 5 received saline (120min each group). Blood flow was measured in the portal vein (PV) and the superior mesenteric artery (SMA) using a Transonics' Doppler ultrasound system. Results Flow decreased in both groups during hemorrhage. SMA flow decreased 44% and 34% while PV decreased 40% and 80% in enalaprilat and saline dogs, respectively. No difference in flow before CRI. Dogs receiving enalaprilat during resuscitation demonstrated a 90% increase in SMA flow and a 74% increase in PV flow. Dogs receiving saline showed a 1.5% decrease and a 21 % flow increase during resuscitation. Conclusions: Enalaprilat during resuscitation improved splanchnic blood flow. A constant rate infusion of enalaprilat in trauma patients might be useful for increasing splanchnic blood flow. (Support: Pfizer, VA Central IA Health Care Sys, DM Research & Ed Corp, Arrow Int'l, Diametrics, IA Space Grant Consortium)

Exploring safety concerns of enalaprilat during resuscitation. R VINCENT, P WALL, L HENDERSON, C BUISING, T RICKERS, A CÁRDENAS, F RAYMOND, B FREEMAN, M WATER, S LICHTENSTEIN, A CHENDRAHSEHKAR, D MOORMAN, G TIMBERLAKE. Surg Ed & Trauma, IA Methodist Med Ctr, Des Moines, IA 50309 and Drake University, Des Moines, IA 50311. Enalaprilat may be useful for improving GI P_iCO_2 in trauma patients; however, concern over its potential for causing hypotension exists. Methods: Five dogs were anesthetized, instrumented, and bled (MAP= 40-45mmHg, then 30-35 mmHg for periods of 30 min). Stepped resuscitation occurred with lactated Ringer's IV at 60ml/kg/hr as a max rate. The resuscitation target MAP's were 40-45mmHg for 30min, 60-65 mmHg for 30min, 60-65mmHg for 30min with a constant rate infusion (CRI) of enalaprilat (0.02 mg/kg/min), then 70-75mmHg with continued enalaprilat. Cardiac index (CI) was measured at the start and end of each interval. Results: 4 dogs survived hemorrhage. The target MAP was achieved and successfully held in each. Average CI at start of enalaprilat =1.6±0.18, after 30min of enalaprilat with MAP=60-65mmHg CI=2.9±0.71, p<0.05. Conclusions: Starting an enalaprilat CRI during moderate hypotension (MAP 60-65mmHg) does not preclude maintenance or an increase in MAP with a limited fluid rate. Additionally, an enalaprilat CRI can increase CI during moderate hypotension. (Support: Pfizer, VA Central [A Health Care Sys, DM Research & Ed Corp, IA Space Grant Consortium, Diametrics, Eagles)

Effect of resuscitation fluid rates on outcome. D DAVIS, P WALL, A CÁRDENAS, T MATTSON, A LARKIN, L WITTKOPF, F RAYMOND, D MOORMAN, G TIMBERLAKE. Surg Ed & Trauma, IA Methodist Med Ctr, Des Moines, IA 50309. Rapid resuscitation (R) with lactated Ringers (LR) has been suggested to contribute to immunosuppression post-hemorrhage.¹ We investigated fluid rate effects on survival. Methods: 30 Wistar-Furth rats were anesthetized; instrumented; hemorrhaged (MAP=35-40mmHg >60min until MAP<30mmHg for >1 0min or <25mmHg for >1 min, or 120min elapsed); and R for 3hr with room temp LR intermittently to keep MAP=75-80mmHg. When running, the LRS rates were 15ml/hr (50.3ml/kg/hr), 30ml/hr (103.9ml/kg/hr), and 60ml/hr (210.9ml/kg/hr). Rats were euthanized at 24hr. Results: (Average ±SEM.)

	#alive start R	#alive 24hr	Δ BE 2hr R	Δ T 3hr R	3hr LR ml/kg
15ml/hr	6	3	5.0 \pm 1.0	-0.7 \pm 0.3	44 \pm 8
30ml/hr	7	2	5.4 \pm 0.8	0.5 \pm 0.4	47 \pm 3
60ml/hr	8	5	7.1 \pm 1.1	1.7 \pm 0.6	89 \pm 17

Rats required LR at max rates for approx the 1st 15, 10, and 5min of R (15ml/kg, 30ml/kg, & 60ml/kg respectively). The slopes of LR received lines in the 15 & 30 rats were not significantly different. The slope of the LR received line was greater in the 60ml/hr rats throughout. Conclusions: The greater improvement in base excess in the rats receiving more rapidly administered LR suggests a benefit to rapid fluids. The increase in body temperature, likely indicating a better resumption of metabolic processes may also support this. (Support: Pfizer, VA Central IA Health Care Sys, Drake) ¹Knöferl *et al.* Shock 9:(suppl):49,1998.