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The Beat Newsletter

College of Medicine

The Beat

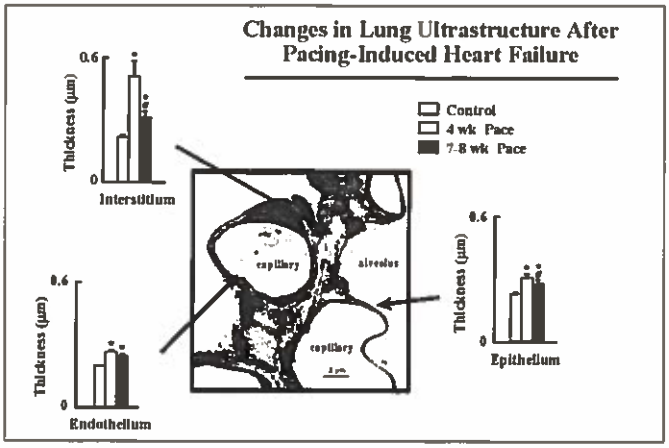
University of South Alabama
College of Medicine

January 2000

PATHOPHYSIOLOGY OF LUNG INJURY SEEN IN CARDIAC FAILURE

Research in the laboratory of Dr. Mary Townsley, Professor of Physiology, has explored mechanisms of adaptive changes in endothelial cell function in an animal model of heart failure. The mechanisms responsible for resistance to pulmonary edema after chronic pulmonary hypertension in heart failure are unclear, but could involve alterations in regulation of pulmonary vascular pressure or regulation of endothelial barrier function, or both. The work in Mary Townsley's laboratory has for sometime focused on pulmonary adaptations to heart failure. A rapid ventricular pacing model of failure, in which a pacemaker generator and transvenous pacing lead are implanted in conditioned dogs using sterile technique under general anesthesia is used. The generator and lead are those commonly used in humans, although the generators have been modified for programming at higher rates than those acceptable for clinical use. Several days after recovery from the implant surgery, the pacemaker is turned on using an external programmer, and the pace rate set to 245 impulses per minute. Echocardiography is used to measure left ventricular shortening fraction (LVSF) and to characterize the progression of failure. Over the course of 1 month, LVSF in the paced dog decreases from ~35% to ~15%, indicative of the development of congestive heart failure. As a consequence, pulmonary venous hypertension and pulmonary edema result. Drs. Jeff Ardell and Walter Johnson were instrumental in helping Dr. Townsley to establish the model of failure. There are many similarities in the clinical picture which develops in this model and that in humans: 1) despite the pulmonary hypertension and interstitial edema, the incidence of alveolar flooding and compromised gas exchange is relatively low; 2) exercise can commonly be tolerated without respiratory distress; and 3) the endocrine pattern includes increases in circulating catecholamines, vasopressin, angiotensin II, renin, and aldosterone. One additional advantage of this model is that pacing rate can be decreased as the pace time increases, allowing the animal to stabilize in an essentially "clamped" failure state. This regimen has been used to maintain animals with impaired, but stable ventricular function, for up to 8 weeks.

One common focus for inquiry in heart-failure-induced pulmonary hypertension is the endothelial contribution to regulation of vascular tone. Indeed, the initial work with this model evaluated pulmonary vascular responsiveness to norepinephrine and the role of endothelial-derived relaxing factors. In these studies, we perfused lung lobes, isolated from



normal animals and those in heart failure, in an *ex vivo* circuit with autologous blood, and found that the increased pulmonary vascular venoconstrictor responses to norepinephrine were not related to loss of endothelial nitric oxide. Dr. Ron McMillon, then a graduate student in the laboratory, used different techniques to evaluate dose-response relationships for ~100-350 µm intrapulmonary bronchial arteries. He dissected these small bronchial arteries from deep within the lung and studied them in an *ex vivo* bath as cannulated, pressurized segments. In contrast to the work on the pulmonary vasculature, he found that the increase in the sensitivity of vessels to α-adrenergic agonists in the bronchial arteries *was* related to a marked loss of endothelial-, and nitric oxide-dependent vasodilator function.

Much less well understood is the state of endothelial barrier function after heart failure. The histopathological observation of basement membrane thickening after long-term heart failure suggested to early investigators in this field that basal endothelial permeability was decreased, yet until recently there was no experimental evidence available to support or refute this claim. In collaboration with Drs. John West and Odile Mathieu-Costello, investigators at UC San Diego, we evaluated pulmonary vascular structure after heart failure. While we can find no evidence for remodeling in larger resistance microvessels or for basement membrane thickening after as much as 2 months of pacing-induced heart failure, we did find significant thickening of all components of the alveolo-capillary barrier. To address

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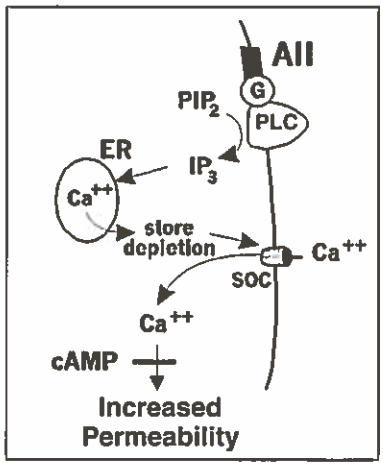
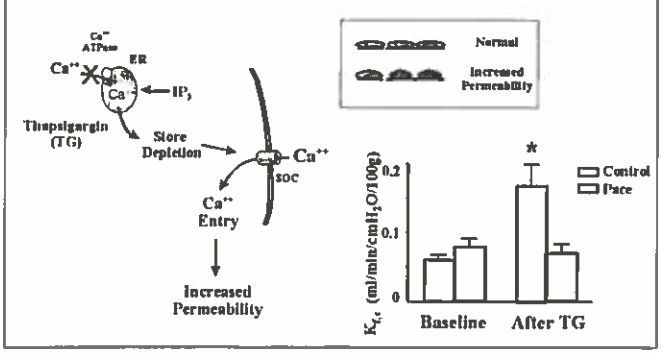
whether this structural change contributes to any alteration in pulmonary endothelial permeability, we asked the questions in isolated, blood-perfused lung lobes isolated from normal animals and those in heart failure, measuring the capillary filtration coefficient ($K_{f,c}$) as a sensitive and specific measure of endothelial permeability. Initially we made the observation that basal pulmonary microvascular permeability, i.e., that in the unstimulated state, remains normal after as much as 8 weeks of pacing-induced heart failure. However, we were surprised to find that after heart failure, the lung resists injury (i.e., an increase in permeability) in response to acute challenge with brief episodes of high vascular pressure. In fact, the pressure threshold for injury was increased from ~30 cmH_2O in the normal lung to ~65 cmH_2O in the lung after heart failure, a response which correlates well with the thickening of the alveolo-capillary barrier.



However, additional work showed that the pulmonary endothelial adaptation is more complex. Dr. Beverly Roy from Division of Neonatology of the Department of Pediatrics joined the lab and found that the normal permeability response to angiotensin II (AII) was lost after 1 month of pacing-induced heart failure. Subsequently, Dr. Claire Ivey, a postdoctoral fellow in the laboratory, together with Dr. Roy began to investigate the mechanism underlying this resistance to injury. They found that the response to AII was related to IP_3-mediated store depletion and could mimic its effect on permeability in normal lung with thapsigargin. Thapsigargin, an inhibitor of the endoplasmic reticulum Ca^{++} ATPase, is used to mimic store-depletion and evoke Ca^{++} entry through the plasmalemmal store-operated Ca^{++} channel (SOC). Dr. Ivey then made the very interesting observation that she could completely block the effects of thapsigargin on pulmonary endothelial permeability using pharmacologic inhibitors of cytochrome P450 epoxygenases, enzymes which metabolize arachidonic acid to produce a family of epoxyeicosatrienoic acids or EETs, including 5,6-EET. Further, she could mimic the effect of thapsigargin on permeability in the normal lung by administration of 5,6-EET alone. This work was made possible through a collaboration with Dr. Al Stephenson at St. Louis University who synthesized EETs for our use. In contrast to the responses in normal lung, neither thapsigargin nor 5,6-EET had any effect on permeability in the lung after heart failure, suggesting some alteration in Ca^{++} signaling.

At present, our working hypothesis is that heart failure results in a the functional "down-regulation" of pulmonary endothelial sensitivity to injury, due to alterations in Ca^{2+} signaling subsequent to store depletion and possibly to alterations in cAMP metabolism. An understanding of this problem is clinically relevant. Clinical outcome for patients with heart failure will be improved if pharmacologic therapies directed at the heart also preserve these protective endothelial adaptations. Ongoing work in Dr. Townsley's laboratory is supported by grants from the National Heart, Lung and Blood Institute (HL39045 and HL61955).

Effect of Thapsigargin (150 nM) on Permeability



SICKLE CELL CENTER HOSTS OPEN HOUSE

The USA Comprehensive Sickle Cell Center held it's first Open House event in September, 1999. The Center invited community leaders, sickle cell clients, math and science classes from the local high school and faculty of the University to the Open House. The Center had over 300 people attend the event.

Speakers for the opening ceremonies were Dr. Steven Goodman, Director; Dr. Johnson Haynes, Associate Director of Adult Clinical Programs; Dr. Betty Pace, Associate Director of Pediatric Clinical Programs; Ms. Rose Peterson, Associate Director of Psychosocial Services; and several community leaders. Ms. Sharron Melton, News Anchor for Channel 15, was Mistress of Ceremonies. Following the opening ceremonies, tours of the sickle cell research labs were conducted.

The event was held to inform the people of south Alabama about the outstanding research and clinical programs performed at the USA Comprehensive Sickle Cell Center.

POINT CLEAR CHARITIES HELP LOCAL CHILDREN WITH CANCER

Representatives from Point Clear Charities, Inc., McConnell Automotive and Gulf Telephone-Gulf Long Distance made a major contribution to the University of South Alabama Children's and Women's Hospital in The Treehouse. "Through the support of Point Clear Charities, our institution is able to improve the lives of children affected by cancer," said V. Gordon Moulton, USA President. The Center will be designed using a submarine theme, providing a fun environment where patients can receive the latest pediatric cancer treatments available. This donation represents the proceeds from the 12th Annual McConnell-Mercedes Cup Polo at the Point.

NIH RESEARCH SUPPORT

The National Center for Research Resources (NCRR) has a unique mission at the National Institutes of Health. Through NCRR, biomedical investigators supported by NIH's disease-oriented institutes can access the resources and technologies they need to conduct research that improves human health.

The diverse research centers and resources that NCRR supports throughout the nation include:

- clinical research and career development at leading academic medical centers;
- biomedical technologies and instrumentation;
- mammalian and nonmammalian models for human disease;
- research infrastructure, including science education, facility construction and renovation, and support to increase research competitiveness of minority institutions and states with limited NIH funding.

These research centers and resources are cost-effective; investigators numbering in the tens of thousands each year share in their use. Moreover, while conducting research at these NCRR-supported centers and resources, many investigators enter into collaborations with scientists from other disciplines who have complementary skills and projects. These partnerships not only extend research dollars, but also enhance scientific ideas. **Dr. Christian R. Abee,** Distinguished University Professor and Chairman, Department of Comparative Medicine is the principal investigator for a Squirrel Monkey Breeding and Research Resource funded by the NCRR program.

The 1999 directory entitled *Comparative Medicine Resources* is designed to help scientists take advantage of these cost-saving, idea-generating resources. For the most up-to-date listing of NCRR-supported comparative medicine resources, visit the NCRR website at http://www.ncrr.nih.gov. A summary of these opportunities is shown in the table below. Other NCRR research resource directories include *Clinical Research Resources* and *Biomedical Technology Resources.* For copies of these or other NCRR publications, or for more information about NCRR-supported activities, contact the Office of Science Policy and Public Liaison, National Center for Research Resources/NIH or email ospio@ncrr.nih.gov

Summary of NCRR Comparative Medicine and Research Grant Opportunities

Research Resources	Research Projects	Career Development and Training	Other Grant Opportunities
◆ Animal (mammalian and non-mammalian) Models; Animals and Biological Materials ◆ Regional Primate Research Centers ◆ Other Primate Resources	◆ Resource-Related Projects ◆ Investigator-initiated Research Projects ◆ Exploratory and Developmental Projects	◆ Special Emphasis Research Career Awards ◆ Midcareer Investigator Awards in Mouse Pathobiology Research ◆ National Research Service Awards/Training	◆ Small Business Technology Transfer - Phases 1 and 2 ◆ Small Business Innovation Research - Phases 1 and 2

Source: NCRR Fact Sheet

ACCREDITATIONS...

The In Vitro Fertilization Laboratory of the Division of Reproductive Endocrinology has been accredited by the College of American Pathology. The Division of Reproductive Endocrinology currently is accredited by the College of American Pathology for Assisted Reproductive Technology and Reproductive Endocrinology. For the last three years, the In Vitro Fertilization Laboratory has ranked among the top programs in the southeast.

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USA Medical Center has been granted accreditation by the American Association of Blood Banks. (AABB). Accreditation follows an intensive on-site assessment by specially trained representatives of the Association and establishes that the level of medical, technical, and administrative performance within the facility meets or exceeds the standards set by the AABB. The AABB sets standards, assesses and accredits blood collection and transfusion facilities, and provides continuing education and information.

If you would like to submit an article for publication, please forward it to:

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FAX (334) 460-6073
Visit "*The Beat*" at
http://southmed.usouthal.edu/com/thebeat.htm

FACULTY NOTES...

Maria C. Soto-Aguilar, M.D., *assistant professor of medicine and pediatrics,* has been invited to serve as a member of the Allergenic Products Advisory Committee of the Food and Drug Administration (FDA). She will advise the Commissioner of FDA on issues that ensure the safety and effectiveness of products used to diagnose, prevent or treat allergies and allergic diseases. Her recommendations will cover product labeling, product licensing and clinical and laboratory studies of products, helping to safeguard the quality and relevance of the FDA's research programs.

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Michael Culpepper, M.D., *professor of medicine and director of the division of nephrology and hypertension,* has been awarded the designation of ASH Specialist in Clinical Hypertension, by the American Society of Hypertension. Dr. Culpepper received the designation from the ASH Specialists' Credential Committee based on his training and experience in treating complex and difficult patients with hypertensive diseases.

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James M. Downey, Ph.D., *professor of physiology,* presented a talk entitled "Role of Kinases in Ischemic Preconditioning" in a symposium on New Insights Into Myocardial Stunning, Hibernation and Preconditioning at the 72nd Annual meeting of the American Heart Association in November in Atlanta, Georgia.

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Donald Herbert, Ph.D., *professor of radiology,* presented an invited lecture at the NIH-sponsored workshop, "Biological Effects and Outcome Analysis of 3D-Radiation Therapy," in Bethesda, MD. Dr. Herbert's lecture entitled *"Useful Models and Adequate Metaphors"* presented an overview of several current issues in biological and clinical modeling: 1) Empitical Bayes model; 2) bivariate probit models of joint response; 3) response surface designs for clinical trials; 4) nonlinear dynamical models of biological systems.

Dr. Herbert also attended a meeting of the Steering Committee for the 6th International Conference on Dose, Time, and Fractionation in Radiation Oncology to be held at the University of Wisconsin in September 2001. Dr. Herbert has been a Co-Chairman and Co-Editor of the Proceedings for the 2nd, 3rd, 4th, and 5th conferences which have been held approximately every four years since 1984.

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Botros Rizk, M.D., *associate professor of obstetrics and gynecology, and director of the division of reproductive endocrinology,* has co-authored a book on Endometriosis. Endometriosis is a disease that effects 15% of women between the ages of 15 to 44. The book outlines the diagnostic and management options for endometriosis based on the research of the authors and advancement in technology.

USA TRANSPLANTATION PROGRAM

Kidney failure is one of the fastest growing diseases in the United States with over 250,000 patients now on dialysis and 17,000 added each year. The only good alternative to dialysis is obtaining a kidney transplant which allows patients to live a more normal life. Although the lifestyle benefits of transplantation have been well established, recent evidence published in the New England Journal of Medicine shows that transplantation adds about 10 years to the life expectancy of patients with kidney failure.

The growing success of kidney transplantation has led to a large discrepancy between organs available for transplant and patients waiting on the List. Over 1000 patients are waiting for a kidney in Alabama while only about 300 will get a new kidney this year. The best alternative to waiting for a cadaver kidney is to find a friend or relative who is willing to give up one of their own. Because of the great advances in drug therapy to prevent rejection, the only match needed today is blood type compatibility. Kidneys from living donors also tend to be of much better quality than those obtained from cadavers and last twice as long on average once they are transplanted (17 versus 8 years).

Patients living along the Gulf Coast now have local access to kidney transplantation at USA Medical Center. The current Program did its first transplant one year ago and has done a total of 20 successful transplants to date. Using a new approach to immunosuppression practiced only in Mobile, not a single patient has gone on to develop even a single rejection episode. Transplant Surgeon, **Dr. Barry Browne** attributes this remarkable success to a team approach which allows for close follow-up and individualized care.

The Transplant Program has been expanding rapidly during the past year and now operates a satellite clinic in Pensacola to serve those living along the Florida panhandle. A second coordinator, Linda Oyler, was recruited to run the Pensacola clinic and to assist Cindy Op't Holt who runs the USAMC clinic. Dr. Egie Emovon will join the Program in January and assume the role of Transplant Nephrologist and recruitment for a second surgeon is well under way. Browne sees the kidney volume growing to 80-100 transplants a year over the next few years as patients and doctors in the region learn more about the services offered at USA.

Pictured above: The USA Transplant Team

ANNOUCEMENTS...

As it name *"Geno-Terato-Epi-Tome"* denotes, this newsletter presents advances in genetics, teratology and epidemiology in brief. *"Geno-Terato-Epi-Tome"* circulates within the university, among healthcare providers, as well as various regions of Latin America and United Kingdom. Readers may send contributions and requests to CCCB 214, Department of Medical Genetics or email to: wwertele.usamail.usouthal.edu. The *"Geno-Terato-Epi-Tome"* is an independent newsletter published by the Department of Medical Genetics.

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An online resource for the College of Medicine Biotechnical Services is now available. The website contains a comprehensive description of each core facility including instrumentation, sample data, facility developments and techniques, and user fees. For more information about these services please visit Biotechnical Services homepage at http://southmed.usouthal.edu/com/rcl.

RECENT PH.D. GRADUATES IN BASIC MEDICAL SCIENCES

Xiao-Tian Yan

Sponsored by Robert N. Lausch, Ph.D., Department of Microbiology and Immunology. Xiao-Tian's dissertation was entitled *"Characterization of Macrophage Inflammatory Protein (MIP)-2 in HSV-1 Induced Corneal Inflammation."*

Scott Hollensworth

Sponsored by Susan LeDoux, Ph.D. Department of Structural and Cellular Biology. Scott's dissertation was entitled *"CNS Cell-Specific Responses To Oxidative mtDNA Damage."*

PREVENTION IS THE BEST HEALTH ADVICE FOR WOMEN

Yvonne Green, director of a leading national women's health office, encourages women to take more responsibility for their own health. She advises them to eat more fruits and vegetables, be physically active and get regular checkups for heart disease, cancer and osteoporosis. This fall she was appointed director of Centers for Disease Control and Prevention - Office of Women's Health after working fifteen years for CDC reproductive health programs. Recently Green has spoken about African-American women's health issues.

African-American women have extra worries when it comes to heart disease, stroke, cancer and childbirth. That's because they are much more likely to die of these conditions than caucasian women.

Social factors such as lower income, less education and less access to medical care are some of the reasons for the disparity, but they don't explain them all. Some of the added risks of African-American women when compared to white women:

- *Heart disease*: 70 percent greater risk of death.
- *Hypertension*: twice the risk.
- *Diabetes:* twice the rate.
- *Pregnancy, childbirth:* fourfold risk of dying.
- *Breast cancer:* 20 percent higher risk of death.
- *Stroke:* 70 percent higher risk of death.

Sources: Mobile Register; Centers for Disease Control and Prevention, National Institutes of Health, American Heart Association

SUMMER RESEARCH PROGRAM FOR MEDICAL STUDENTS

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Call for Proposals

This notice is a reminder for the call of proposals for the summer research program for medical students. All faculty members are encouraged to submit well designed and competitive projects which will provide a quality research experience for incoming and first year medical students. The summer research program starts in June. The deadline for receipt of research proposals is February 29, 2000. Please forward your proposal to the Senior Associate Dean's Office, CSAB 170.

ETHICS IN RESEARCH TRAINING COURSE

The National Institutes of Health and the Department of Mental Health Law and Policy at the University of South Florida will be offering a course in 2000 entitled "Ethics in Research: An Intensive Training Course Focusing on Behavioral Health Services". For details, see http://www.fmhi.usf.edu/mhlp/ethics/ethics.html.

More information, including scholarships and registration fees will be posted on the website. Anyone interested in this training should send their name, address and e-mail address to: Kelly M. Lyon, B.A., Coordinator, Department of Mental Health Law and Policy, University of South Florida, Fax: (813) 974-9327.

NEW AWARDS: FROM THE NATIONAL INSTITUTES OF HEALTH

A five year grant has been awarded to **Dr. Robert Lausch**, *Professor of Microbiology and Immunology*. The grant is entitled "Role of MIP-2 in HSV-1 Induced Corneal Inflammation.", Funding of the grant is $963,102.

Dr. David Dean, *Associate Professor of Microbiology and Immunology* was awarded a $60,000 grant from the NIH for studies aimed at the Development of Nuclear Targeting DNA Vaccine Vectors. The STTR grant involves collaboration between university scientists and the private sector. Vical, Inc., a California based biotech company, is the industry partner on the project.

A five year renewal has been awarded to **Dr. Herbert Winkler**, *Professor and Vice Chair, Department of Microbiology and Immunology*. The title of the grant is *Permeability of the Epidemic Typhus Rickettsia*. Total funding during the grant period is $2,396,406.

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