

Academic Physician Quarterly

A DEPARTMENT OF MEDICINE BULLETIN



UF UNIVERSITY of FLORIDA
 College of Medicine
 Jacksonville

INSIDE THIS ISSUE

Chairman's Message

..... Cover

Focus

..... Page 2

GME Corner

..... Page 4

A Clinical Case

..... Page 4

RX Update

..... Page 5

News & Notes

..... Page 5

UF & Shands Brand

..... Page 6

CHAIRMAN'S MESSAGE

Dear Colleagues;

The Department of Medicine at the University of Florida College of Medicine-Jacksonville is launching a quarterly newsletter. This first issue coincides with the start of a new season that we hope will bring peace and prosperity for all.

The purpose of this endeavor is to keep the UF & Shands community and friends posted as to the developments within a department that cares for almost 40% of patients admitted to the hospital. It is understandable that the changes within the Department of Medicine affect the operations of most of other departments and therefore it's everyone's business to keep abreast of the accomplishments within Medicine. In addition, to this strategic goal, the newsletter will also have an educational goal and will serve as a vehicle to promote collegiality. To achieve these goals, each issue will have an interesting case presentation, an update on a new drug, highlight our ongoing efforts in clinical, teaching and research missions and report on news and announcements of interest to our health care community at large.



One of the early tasks at hand was to choose an appropriate name for this newsletter. The decision of the editorial team was to call this newsletter Academic Physician Quarterly to highlight the academic mission of the Department. If you have other alternative suggestions please let me know and we will share those suggestions with the readership for additional input.

As we celebrate the arrival of Spring please join me in welcoming the launch of this new departmental vehicle of communication.

*Arshag D. Mooradian, M.D.
 Professor of Medicine
 Chairman, Department of Medicine*

**Advanced Cardiovascular Care
Probing the Potential of Gene
Therapy**

Marco Costa, M.D.

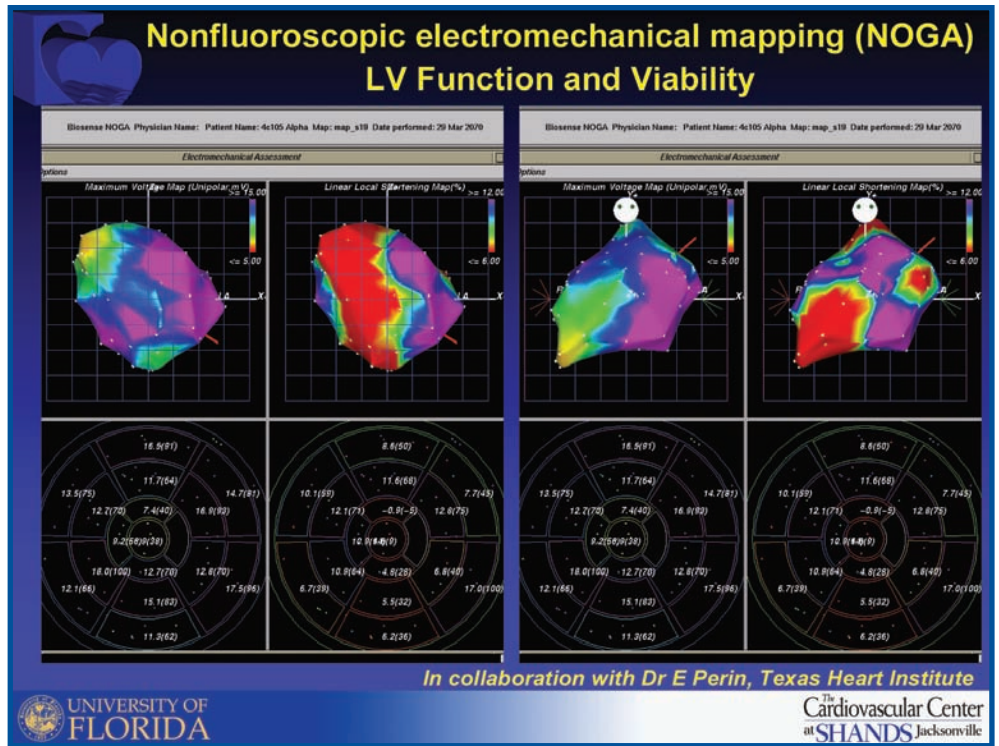
Division of Cardiovascular Diseases



Morbidity and mortality from congestive heart failure continues to increase, despite, and perhaps because of, decreases in

mortality associated with coronary artery disease and acute myocardial infarction in developed countries. Recent advances in the pharmacological and non-pharmacological therapies of CHF including costly procedures, such as surgical cardiomyoplasty, heart transplantation, bi-ventricular pacing, implantable cardioverter defibrillators (ICD) and left ventricle assist devices, have been unable to produce major survival benefits for patients with CHF. In recent years, angiogenesis, which refers to the formation of new arteriolas lacking developed media from pre-existing vessels, has been proposed as an alternative treatment for patients with severe CAD, CHF and poor candidates for current revascularization strategies. Further, angiogenesis may become an adjunctive strategy to other revascularization strategies, such as PCI and CABG, in patients with advanced CAD.¹

The major physiologic stimuli to angiogenesis include tissue hypoxia and inflammation. Initial attempts to promote angiogenesis used laser or other mechanical means to create multiple small holes in the



endocardium. The use of growth factor proteins such as vascular endothelium growth factors or genes encoding these proteins to promote angiogenesis has been under study for last decade. There is increasing evidence that cell transplantation may improve perfusion and contractile function of the damaged myocardium²⁻⁵. Whether the mechanism of action involves myocardium repopulation or neovascularization, or ideally both, remains to be determined. Transplanted cells may also stimulate the resident myocytes to improve their contractility by the release of cytokines and improvement in blood flow. Our understanding on stem cell biology has advanced considerably in the past years. Ability to direct the plasticity of precursor stem cells has lead to the hope that severe heart disease might be ameliorated by cell transplant therapy⁶. The demonstration of both resident and circulating stem cells committed to cardiac cell lines opened a new avenue in cardiovascular research⁷. Progenitor endothelial cells (PEC), which express

CD34 and CD 133(AC133) antigens, are high in the list of candidate cells for promoting angiogenesis. These cells have the potential to differentiate into vascular endothelial cells and blood cells and ultimately promote vasculogenesis, a phenomenon not yet demonstrated in adult human hearts. PECs can be identified in adult peripheral blood, bone marrow and human umbilical cord blood. The ability to delivery of high concentrations of cells, angiogenic proteins or genes within the target myocardium represents another important aspect of angiogenesis therapy for cardiac disease. Percutaneous approaches using direct intramyocardial injection catheters guided by 3D imaging and non-fluoroscopic electromechanical mapping (NOGA, Biosensor Webster)⁴ offers the advantage to assess viability of target sites prior to each injection and assure precise intramural delivery in a safe and minimally invasive manner.

Continued on page 3

Areas supplied by totally occluded epicardial vascular beds can be targeted by this method. However, this technology is costly and available in limited centers worldwide.

The division of cardiology at the University of Florida, College of Medicine Jacksonville is committed to advance our knowledge and develop new therapeutic modalities for patients with advanced cardiac and peripheral vascular disease. We have developed a comprehensive research program in the field of angiogenesis and cell therapy. The molecular component of the program is dedicated to understanding the functional profile of endothelial progenitor cells (EPC = CD34+ cells) in patients with diabetes mellitus and/or CAD and we have conducted an initial clinical investigation which involved 54 patients. Our group is also exploring new approaches to stimulate angiogenesis. We proposed the concept of injecting antibodies against circulating progenitor cells directly into the myocardium to recruit cells in situ. A pilot experimental study was performed in collaboration with investigators (Dr Emerson Perin) at the Texas Heart Institute, Houston, TX.

We recently initiated collaboration with Professor Takayuki Asahara, MD, PhD, Director of Regenerative Medicine and Research Kobe Institute of Biomedical Research and Innovation, who first described the presence of circulating progenitor cells in humans. We are currently supporting clinical trials testing PECs for the treatment of cardiac disease and peripheral vascular disease in Japan. Future plans are

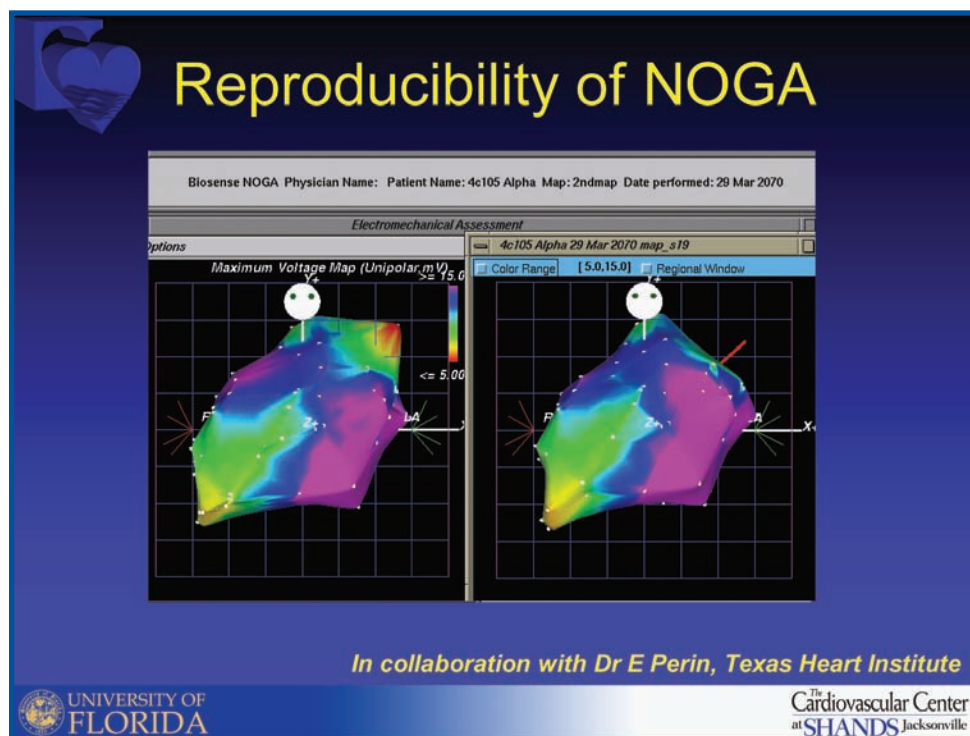
to establish a center for expansion of progenitor cells which would facilitate the implementation of angiogenesis therapy in clinical practice.

Our Institution was the first in Florida to apply transmural injection of gene therapy to promote angiogenesis in patients with advanced coronary artery disease. We recently started the first U.S. multicenter study for transmural injection of bone marrow derived CD34+ stem cells to promote angiogenesis in patients with advanced CAD. This clinical study uses the NOGA catheter technology to guide and monitor cell delivery.

Finally, our division, through a collaborative effort between the Cardiovascular Imaging Core Laboratories and the department of Radiology developed a systematic approach to quantify MRI data, which is currently being applied to various angiogenesis clinical trials. The MRI data from the first US trial testing the feasibility of intramyocardium injection of BMC in patients with CHF, conducted at the Texas Heart Institute, is being analyzed by our Core Laboratory. Another collaborative clinical effort has been initiated with the Minneapolis Heart Institute (Dr Timothy Henry) to evaluate myocardial perfusion and function using MRI in patients who underwent different forms of angiogenesis therapy.

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**N. Stanley Nahman, Jr., M.D. (Program Director),
Olga Petrucelli, M.D. and Arpitha Ketty, M.D.
(Associate Program Directors)**

The office of Graduate Medical Education seeks to advance all facets of the academic mission, but with particular emphasis on education. Part of the educational program includes development of critical thinking through literature reviews in monthly journal clubs, and facilitating the acquisition of analytic tools for research and investigation.

In the latter area, the institution offers Dean's Fund Research Grants for trainees that may award up to \$5,000 in support. In August 2006, the Department received five 5 such grants, all of which were spearheaded by resident investigators. The spectrum of funded studies was diverse and included an assessment of kidney function in older patients with sickle cell disease, production of a video articulating an approach to end-of-life decisions, and the role of hepatitis C in promoting

bacteremia in dialysis patients. All projects are funded for one year and are currently in progress.

In other areas of research, the program's mega-team approach to the allocation of resident manpower was highlighted in an oral presentation at the Southern Society of the American Federation of Medical Research's Regional Meeting on February 8 through the 10th in New Orleans. We anticipate that this presentation will provide the basis for a follow-up publication documenting the Department's experiences with this novel approach to organizing resident ward teams on inpatient medicine services.

In summary, the office of Graduate Medical Education offers a variety of research opportunities, all of which are designed to provide a meaningful exposure to the challenges and rewards of original research, as well as groom forward-thinking clinicians who will always seek improved, and novel, approaches to patient care or education.

A CLINICAL CASE

Erik Lowman, D.O., Chief Resident

Macromelia Masquerading as an Acromegaloid Syndrome in an Adult with Klippel-Trenaunay Syndrome

Klippel-Trenaunay syndrome (KTS) is a rare congenital condition that belongs to a family of human disorders characterized by tissue overgrowth¹. Classically the syndrome presents as a triad of vascular malformations, cutaneous hemangiomas and bone or soft-tissue hypertrophy usually affecting one extremity. The tissue hypertrophy in this syndrome is typically localized and asymmetrical. In this communication we describe a case of this disease in an adult patient with symmetrical macromelia suggestive of an acromegaloid syndrome. The serum levels of growth hormone and insulin like growth factor one (IGF-1) were normal.

In a series of 252 patients with KTS, capillary malformations (port-wine stains) were found in 98%, varicosities or venous malformations in 72%, and limb hypertrophy in 67%. All three features of KTS were present in 63% of patients studied, and 37% had two of the three features¹. Our patient had all the three components of the syndrome.

In addition he had substantial lymphedema in left lower extremity. Lymphedema is not common although it has been previously described.

In patients with vascular disease two mutations have been described that have pathogenetic significance. One mutation is the chromosomal translocation t(5;11) which increases the transcription of VG5Q, a protein that acts as a potent

Continued on page 5



Figure: The hands of the patient shown in comparison to an average adult hand in the middle illustrating the symmetrical macromelia, a common feature of acromegaloid patients.

angiogenic factor². The second is a functional mutation of E133K that enhances the angiogenic effect of VG5Q. Thus, VG5Q is a susceptibility gene for KTS, and increased angiogenesis is a molecular pathogenic mechanism of this syndrome². The IGF2 over expression has been implicated in the etiology of the tissue hypertrophy observed in KTS³.

The recognition of this syndrome will help avoid any unnecessary and extensive work up for acromegaly.

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NEWS AND NOTES

Internal Medicine Residency Program Receives First Endowment

The Anne and Max Michael, Jr. Education fund is founded by Mrs. Anne Michael in memory of her late husband, Dr. Max Michael, Jr. who was the first Dean in the Jacksonville campus from 1962-1985.

This fund awards a hand crafted wood lacquered rocker with a gold screen printed seal of the University of Florida from 1873, to our graduates who complete a three year residency training program in Internal Medicine.

Mrs. Michael was at the Department of Medicine Annual Award Banquet on June 2, 2006 at The River Club, to present to the first graduating class to receive these special rockers with Dr. Stan Nahman.

RX UPDATE

Gliptins: A New Therapeutic Option for Diabetes

These agents are selective inhibitors of dipeptidyl peptidase 4 (DPP-4), the enzyme that degrades incretins as well as other select peptides. The incretins, such as glucagon -like peptide-1 (GLP- 1) or glucose-dependent insulinotropic peptide (GIP) are secreted by the gut following nutrient ingestion and have multiple biologic effects including, augmentation of insulin secretion, inhibition of glucagon secretion, inhibition of gastric emptying and enhancing satiety.

Vildagliptin and sitagliptin (approved by FDA 10/2006) are two agents that belong to this class. In clinical trials they have been shown to be effective as either monotherapy or as an adjuvant therapy to metformin, thiazolidenediones and possibly with insulin in a select group of patients.

The advantages of these agents include lack of significant risk of hypoglycemia, lack of weight gain and possibly preservation of pancreatic beta cells. The disadvantages include cost, lack of long term safety data, and uncertainty as to the optimal patient population to target.



Figure - N. Stanley Nahman, Jr., M.D. (Program Director) and Mrs. Anne Michael

UF&Shands Jacksonville

The University Of Florida Health System

From ancient times when stone masons began cutting their trademark signatures into the house facades

they created, branding has been essential to society. But unlike those ancient artisans, a modern brand is not just a logo. Instead, a brand is more of a “feeling” than anything tangible. This “feeling” is what a properly developed brand represents to its audience and how successful brands are built. Brands like Volvo or Nike have been carefully crafted over the years to symbolize “safety” and “competitive sports” respectively. Those carefully created brands enjoy a loyal audience as well as a higher value relative to a lesser-known competitor. What the UF&Shands brand is now doing is no different. In 2004, we began an awareness campaign of the brand which was the combination of the

two entities – The University of Florida Health Science Center and Shands HealthCare.

The next phase of the branding campaign will spotlight the power of “&”, and what we have accomplished by working together. Amazing stories are being told every day in our corridors – stories of medical breakthroughs, better treatment options and strong patient relationships. Just as the ampersand links our organizations, the symbol is used as a visual theme throughout the campaign to highlight our important connections. Filming and photography took place in October and November 2006, and the campaign launched in January. Television and radio spots will run on local broadcast and cable channels, supported by ads in major newspapers and regional magazines.

Next time you see the ads, perhaps you’ll see yourself or one of your colleagues and feel your contributions to the “Science of Hope”.

Editorial Staff: Arshag D. Mooradian, M.D., N. Stanley Nahman, Jr., M.D. and Lorna Matos

904-244-8846; fax: 904-244-8844
Jacksonville, FL 32209-6511
Department of Medicine
653-1 West Eighth St.
Jacksonville

College of Medicine

UNIVERSITY of FLORIDA



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