

Beta-Blockade Therapy and Adrenergic Receptor Polymorphisms in Heart Failure

by Ronald Zolty, MD

THE EMERGING FIELDS OF PHARMACOGENETICS AND PHARMACOGENOMICS INVOLVE THE SEARCH FOR GENETIC POLYMORPHISMS THAT INFLUENCE HUMORAL RESPONSE TO DRUG THERAPY.

These disciplines offer the promise of developing individualized, tailored drug therapy on the basis of genotype, thus increasing the likelihood of achieving treatment goals while limiting adverse effects from drug therapy.

Heterogeneity of clinical response to medical therapy, in terms of treatment efficacy, may be explained by multiple variables including: the etiology and severity of the disease being treated, drug interactions, patient factors such as age, nutritional status, renal and liver function, co-morbidities and compliance with treatment regimens. Despite the potential impact of these clinical variables on therapeutic efficacy, it is now recognized that inherited genetic variation in the metabolism and disposition of drugs, and genetic variation of the targets of drug therapy (such as receptors), play a significant role in individual response to medical therapy.

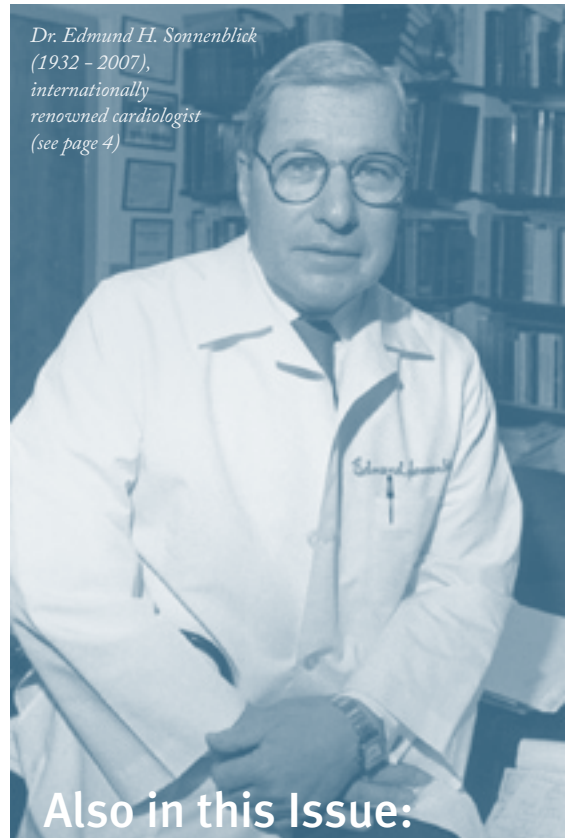
Data from the Human Genome Project found that small and even modest-sized nucleotide deletions, insertions, and rearrangements contribute to diversity within the genome. These variations known as SNPs, or single nucleotide polymorphisms, represent the largest class of inter-individual genetic variation. The majority of these genetic polymorphisms are likely of little clinical importance.

A subset, however, appear to have functional consequences influencing the interplay of genetic and environmental factors on phenotype, including response to medications.

Heart failure (HF) represents a major public health problem because of its high prevalence, unfavorable outcome, and economic burden. In HF, activation of the adrenergic system has been shown by numerous studies to be deleterious to the heart in the long term. Several large randomized trials have confirmed the beneficial role of β -blockade in improving left ventricular ejection fraction (LVEF) and mortality in HF patients. However, in spite of the clear benefits of β -blockade, clinical response to β -blocker therapy displays a high degree on inter-individual and inter-ethnic variation. Underlying genetic variation in adrenergic mechanisms is one potential explanation for this variability in response. The β_1 and α_{2c} adrenergic receptors (ARs) play a critical role for maintenance of homeostasis in the human heart. Certain β_1 (specifically at amino acid position 49 and 389) and α_{2c} (deletion 322-325) AR polymorphisms have been shown to act as disease modifiers in HF. Thus, we hypothesized that the different inter-individual response to β -blockers might

(Continued on back)

Dr. Edmund H. Sonnenblick
(1932 - 2007),
internationally
renowned cardiologist
(see page 4)



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Co-Directors:

Richard N. Kitsis, MD
*Dorros Chair
Professor and Chief
Division of Cardiology*

Robert E. Michler, MD
*Belkin Chair
Professor and Chairman
Department of
Cardiothoracic Surgery*

Heartline Editors:

Chris Snyder
Melissa Crissman
Joanne Choi

Correspondence:

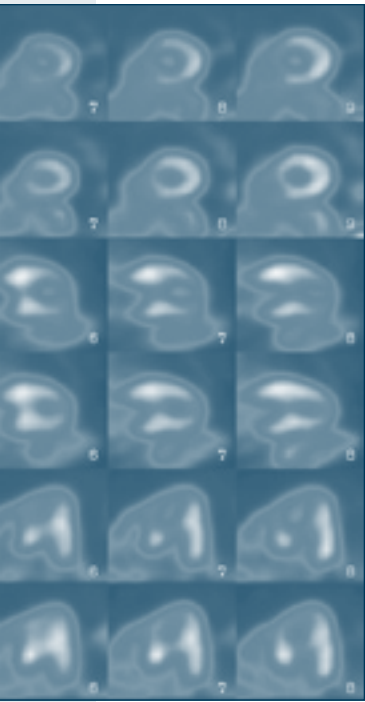
Marketing Department
111 East 210th Street
New York, NY
10467-2490

tel. 718 920 7823
fax 718 405 1938

Cardiac Imaging with Radiotracers: SPECT and PET by Mark Travin, MD

CARDIOVASCULAR DISEASE, MOSTLY FROM CORONARY ARTERY DISEASE, IS THE LEADING CAUSE OF DEATH IN THE UNITED STATES, CLAIMING THE LIVES OF CLOSE TO 900,000 PEOPLE ANNUALLY, AS MANY AS THE NEXT FOUR LEADING CAUSES COMBINED.¹

The good news is that over the past decade the death rate from cardiac disease has declined over 20%, in large part the result of improved therapies and greater public attention to cardiac risk factors. Cardiac imaging has also played a crucial role by providing accurate diagnoses of the presence, extent, and severity of coronary disease, thereby helping to better direct patient management. Among cardiac imaging techniques, stress radionuclide myocardial perfusion imaging (MPI) has become a standard for diagnosis, risk stratification, and coronary disease management. Stress MPI can separate low from high risk patients better than clinical data and other cardiac imaging techniques. As opposed to alternative imaging methods, such as invasive cardiac catheterization and newly developed noninvasive multidetector CT coronary angiography that customarily look only at anatomy, MPI assesses the functional significance of coronary disease, thus often making this technique better at identifying patients at risk of an adverse cardiac event.



New technologies promise to enhance further the clinical utility of MPI. For most of its approximately 30 year history, MPI has used single photon emission computed tomographic (SPECT) imaging techniques and tracers, such as thallium-201 or Tc-99m sestamibi. Although cardiac SPECT MPI has served patients well, it is impaired both by technical issues and the limited cardiac imaging molecules that can be synthesized. A similar imaging technique, cardiac positron emitting tomography (PET), has for many years been used mostly in research, but in part because of technologic developments, PET has been

moving into the clinical mainstream. Recent studies have shown that with visual interpretation techniques, cardiac PET with N13-ammonia or rubidium-82 is more accurate than SPECT for diagnosing coronary disease, and that



Hybrid PET/CT camera.

like SPECT, PET can effectively risk stratify patients. An important potential of cardiac PET is that it can quantify coronary blood flow. Development of PET quantitation promises great improvement in diagnostic accuracy, including the ability to identify every patient with high risk disease, as well as allow detection of patients with subclinical disease whose response to medical therapies can be monitored before a serious problem occurs.

The variety of imaging molecules that can be developed with PET are numerous. Cardiac PET already has the ability to detect metabolically active regions in patients with severe congestive heart failure. PET radiotracers that can image the underlying molecular processes of coronary and other cardiac diseases are under active investigation, thereby making PET a promising tool that should make a dramatic impact on the #1 cause of death in much of the world.

Dr. Mark I. Travin is the Director of Cardiovascular Nuclear Medicine at Montefiore Medical Center and Professor of Clinical Nuclear Medicine and Clinical Medicine at Albert Einstein College of Medicine

1. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al. Heart disease and stroke statistics — 2007 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007; 115: e69-e171.

Over the past decade the death rate from cardiac disease has declined over 20%.

Cardiac Recovery at Montefiore

A LITTLE MORE THAN A YEAR AFTER CMS EXPANDED THE INDICATIONS FOR CARDIAC REHABILITATION MORE PATIENTS ARE BEING REFERRED FOR CARDIAC REHABILITATION FROM A VARIETY OF SPECIALTIES INCLUDING INTERNAL MEDICINE, FAMILY PRACTICE, AND GENERAL PRACTITIONERS.



Dr. David Prince, Director of the Cardiac Recovery Program at Montefiore-Einstein Heart Center explained this trend stating, “as awareness of cardiac rehabilitation continues to grow the desire of primary care providers to refer patients continues to increase. It makes sense that internists and family physicians would refer their patients to cardiac rehabilitation programs as secondary prevention, since they are safe and effective. Cardiac rehabilitation is a structured behavior modification program — and behavior modification is at the core of preventive medicine.”

Although in the past many primary care providers depended on their colleagues in cardiology to manage

all aspects of secondary prevention. Dr. Prince has noted a shift in referral patterns following the CMS decision. “Primary care providers today are very proactive when it comes to preventive medicine and they understand the importance of exercise. Many of them are active exercisers themselves and they know patients will not initiate or stick with an exercise program on their own, especially when there is fear or anxiety involved. The CMS decision has given increased emphasis to the importance of these programs. There is now abundant research that demonstrates the importance and cost effectiveness of cardiac rehabilitation programs and primary care providers want to practice evidence based medicine.”

The Montefiore-Einstein Heart Center cardiac rehabilitation facility is located on the East campus close to Jack D. Weiler Hospital. “We accept referrals from primary care providers as well as cardiologists. In the past two years I have also seen more and more patients referring themselves after they or their family members read about cardiac rehabilitation online.” Dr. Prince believes that patients today are better informed due to accessibility of information on the internet. “Even if a patient is not internet savvy, they have kids or family members who are. We get calls every week from family members who want to get their family members enrolled.”

Following a two year review process, the Centers for Medicare and Medicaid Services concluded

that, “The evidence is adequate to conclude that cardiac rehabilitation is reasonable and necessary following acute myocardial infarction (AMI), coronary artery bypass graft (CABG), stable angina pectoris, heart valve repair/replacement, percutaneous transluminal coronary angioplasty (PTCA), and heart or heart-lung transplant.” The diagnoses of PTCA, valve replacement, and heart or heart-lung transplant were new additions to the criteria to meet medical necessity. “With this proposed coverage decision, CMS seeks to expand coverage to a greater number of beneficiaries with cardiac illness,” said CMS Administrator Mark B. McClellan, MD, PhD. “But just as importantly, we hope that our proposed decision will raise the public’s awareness regarding cardiac rehabilitation services in general.”

Dr. David Prince is the Director of the Cardiac Recovery Program at Montefiore Medical Center. For more information please go to www.montefiore.org/Heart/CardiacRehabilitation.

1. Proposed Decision Memo for Cardiac Rehabilitation Programs. CMS. 12/27/05.
2. Medicare expanding coverage and services for cardiac rehab. SeniorJournal.com 1/5/06. <http://seniorjournal.com/NEWS/Medicare/6-01-05-MedicareExpanding.htm>



**FIFTY YEARS
OPEN HEART
SURGERY AT
MONTEFIORE**

IN MEMORIAM

Edmund H. Sonnenblick, MD

December 7, 1932 - September 22, 2007

by Richard N. Kitsis, MD

THE MONTEFIORE-EINSTEIN HEART CENTER AND THE WORLD LOST A GIANT IN THE FIELD OF CARDIAC CARE DURING THE FALL OF 2007. DR. EDMUND H. SONNENBLICK, A CARDIOLOGIST WHOSE RESEARCH FORMED A BASIS FOR THE MODERN TREATMENT OF HEART FAILURE, WHICH HAS EXTENDED THE LIVES OF MILLIONS OF PEOPLE, DIED AT THE AGE OF 74 AT HIS HOME IN CONNECTICUT.

The following is a composite of remarks that Dr. Richard N. Kitsis, co-director of the Montefiore-Einstein Heart Center, delivered upon the posthumous bestowing of the American Heart Association's Research Achievement Award to Dr. Sonnenblick, and from a memorial service that took place in New York earlier in October of 2007.

Dr. Sonnenblick was different things to each of us: loving husband; devoted father, father-in-law, and grandfather; caring physician; towering scientist; nurturing teacher and mentor; kind human being; loyal friend; and gentleman.

Dr. Sonnenblick was truly a giant in the field of cardiology. One of the most important cardiovascular physiologists of the 20th century. A legend and icon. In 1961, when he was only 29 years old, he carried out fundamental scientific studies that revealed for the first time the mechanical principles that govern cardiac function. This research was performed at the National Heart Institute — now known as the National Heart, Lung, and Blood Institute — of the National Institutes of Health. Working first with Dr. Stanley Sarnoff and later with Drs. Eugene Braunwald and John Ross, Jr., Dr. Sonnenblick delineated the

mechanical underpinnings of cardiac function. The resulting concepts of preload, afterload, and contractility are used on a daily basis by physicians throughout the world.

As impressive as all of this is, he then proceeded to use the electron microscope, a new tool at the time, to go one step further. He determined how the alignment of contractile proteins in heart muscle cells explains some of the mechanical principles that he had discovered.

Dr. Sonnenblick then applied these basic concepts to human disease. His ideas contributed heavily to the development by others of ACE inhibitors as a treatment for heart failure. Moreover, Dr. Sonnenblick's understanding of cardiac physiology was so deep that it often gave him the courage to go against prevailing dogma. For example, based on physiology, he theorized that β -blockers, which were then contraindicated in heart failure, might actually be beneficial in this syndrome. This proved correct. As we all know, the combination of ACE inhibitors and β -blockers has extended the lives of countless heart failure patients.

The most ground-breaking advances in clinical medicine often begin with

novel biological insights. It is rare, however, that a single scientist is able to both make the fundamental discovery and translate it into clinical practice to save lives. Dr. Sonnenblick was able to do this, and this is an important part of his legacy.

During his career, Dr. Sonnenblick trained more than 300 individuals in clinical cardiology and cardiovascular research. He was an exceptionally patient and supportive mentor. In the mid-1980s, basic cardiovascular research underwent a fundamental shift from investigations that were primarily physiological in nature to ones that melded physiology with molecular biology and genetics. Although a physiologist, Dr. Sonnenblick showed exceptional vision and foresight when, in collaboration with Drs. Leslie Leinwand and James Scheuer at Albert Einstein, he helped to create what was perhaps the world's first training program in molecular cardiology. The graduates of this program include multiple outstanding scientists and leaders in cardiology and cardiovascular research.

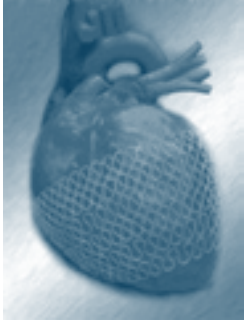
Dr. Richard N. Kitsis is co-director of the Montefiore-Einstein Heart Center.



The Peerless-HF Study; A Novel Treatment for Advanced Heart Failure

by Simon Maybaum, MD

HEART FAILURE IS A CONDITION THAT AFFECTS MORE THAN 5 MILLION PEOPLE IN THE UNITED STATES, WITH 550,000 NEW DIAGNOSES EACH YEAR.



PEERLESS-HF / Paracor Medical

- HeartNet™ device: ventricular support to reduce wall stress
- Primary endpoints: peak vO₂ and 6-min walk at 6 months; quality of life questionnaire
- Major inclusion criteria:
 - Symptomatic heart failure ACC/AHA stage C
 - LVEF < 35%
 - LVEDD < 85 mm, LVEDDi < 40 mm/m²
 - Peak vO₂ 10.0-20.0 mL/min/kg
 - Heart failure duration > 6 months

<http://www.paracor.com>

As the disease progresses the heart may become enlarged and weak so that it can no longer pump blood efficiently to the rest of the body, affecting the ability to perform even simple activities. Heart failure medications can significantly improve symptoms and prolong life, however, some patients become refractory to these therapies. Some may eventually be required to receive a heart transplant. As a result, new drug and device studies are continuously designed to help this patient population, and exploring promising approaches to treating heart failure continues to be a priority at the Center for Advanced Cardiac Therapy at Montefiore-Einstein Heart Center.

Our center is currently participating in a novel study for heart failure patients. The PEERLESS-HF trial, sponsored by Paracor Medical, is a multi-center device study to test the safety and efficacy of the HeartNet™ Ventricular Support System compared to standard heart failure therapy. This innovative technology consists of an elastic nitinol mesh implant that is wrapped around the patient's heart to provide physical support for the walls of the heart; it is implanted via a deployment system that requires a much less invasive

surgical operation than open heart surgery. By reducing wall stress, the implant may help deter or reverse the heart enlargement process present in heart failure patients.

The PEERLESS-HF study is conducted in New York exclusively at the Montefiore-Einstein Heart Center's Center for Advanced Cardiac Therapy by Dr. Simon Maybaum and Dr. David D' Alessandro. Our first patient enrolled, underwent the HeartNet™ implant in late October 2007 and has done extremely well.

We continue to evaluate patients who express interest in the trial and/or may benefit from this procedure. Please support us by considering this clinical trial for your advanced heart failure patients who are not responding to conventional therapy. For more information about our center and the PEERLESS-HF study, please contact Audrey Kleet, NP at 718-920-2626.

Dr. Maybaum is co-director of the Center for Advanced Cardiac Therapy at Montefiore-Einstein Heart Center.

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Beta-Blockade Therapy *(continued from cover)*

be due to genetic polymorphisms of the $\beta 1$ and α_{2c} AR genes.

600 patients with LVEF $\leq 40\%$ from any etiology were selected from the HF Clinic at the University of Colorado Hospital and correlation between the different $\beta 1$ and α_{2c} -AR polymorphisms and LVEF response to β -blockade therapy was evaluated.

We demonstrated in this retrospective study:

- 1) A significant association between $\beta 1$ AR genotype and the magnitude of improvement in LVEF in patients with HF when treated with β -blockers. In other words, $\beta 1$ AR polymorphisms are predictive of improvement in LVEF in patients who otherwise present with similar clinical features, including LVEF and similar β -blocker usage. Specifically subjects that were Arginine389 homozygous and/or Glycine49 had a greater LVEF improvement compared with Glycine389 carriers and/or Serine49 carriers.
- 2) A strong correlation between the different $\beta 1$ -AR haplotypes (based on codon 49 and 389 polymorphisms) and the difference in the LVEF improvement when treated with β -blockers.

- 3) The combination of the $\beta 1$ Arginine389 homozygous and α_{2c} Deletion322-325 demonstrated a significant change in LVEF on β -blockers compared to $\beta 1$ Glycine389 carrier and α_{2c} wild-type.

In summary, in HF these different $\beta 1$ and α_{2c} AR polymorphisms were shown to be important predictor of LVEF improvement with β -blockers.

Currently at The Montefiore-Einstein Heart Center we are conducting similar studies, mainly in the African American and Hispanic HF populations, to determine if the results obtained in Colorado are reproducible in other ethnicities.

In conclusion, pharmacogenomics has the potential to revolutionize the field of heart failure therapy. The preceding examples of genetic polymorphism relevant to the treatment of heart failure with beta-blockers illustrate the promise of this exciting area. The study mentioned in this article provides a scientific basis for the use of genomic information for the individualization of heart failure therapy based in a patient's genetic profile.

For more information, please contact Dr. Zolty's office at 718-430-3544.

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