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Genomics-Based Test Replaces Heart Biopsy

Based on the CARGO study, a blood test is replacing endomyocardial biopsy as the gold standard for detecting organ rejection after heart transplantation.

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Since the 1970's, heart transplant patients have had to regularly undergo an invasive, uncomfortable, and potentially risky test for signs of rejection, a leading cause of death among heart transplant recipients. The test, endomyocardial biopsy, or EMB, involves inserting a catheter into a vein in the neck and threading it into the heart, so that a tiny amount of the heart muscle can be sampled for analysis. Now, a quick, easy-to-administer blood test is rapidly replacing EMB as the gold standard for diagnosing rejection of the donor heart.

The test, a product of a five-year, multicenter study conducted with biomedical company XDx, was based on the hypothesis that a genetic test could detect the absence of rejection in heart transplant recipients. "We believed that using the knowledge gained by the mapping of the human genome, it might be possible to detect gene expression variations that correspond to immune activity during rejection. If so, these changes could be identified by testing a regular blood sample," explains Mario C. Deng, MD, Director of Cardiac Transplantation Research at Columbia University, Department of Medicine, Division of Cardiology, and Co-Principal Investigator of the Cardiac Allograft Rejection Gene Expression Observational study (CARGO).

CARGO proceeded in three phases, and involved testing of over 600 patients in eight U.S. centers.

PHASE 1: GENE DISCOVERY

During the first phase of the study, the researchers determined the genetic changes associated with the immune process involved in rejection after heart transplantation. They constructed DNA microarrays and analyzed over 7000 genes identified in medical literature as involved in immune activation by cells known as leukocytes. In contrast to older methods of studying the activity of single genes, powerful DNA microarrays arrange the entire genome on a single chip, and can provide a picture of the activation status of thousands of genes at once. Screening of more than 7000 genes during Phase 1 refined the researchers' gene selection to 252 candidate genes.

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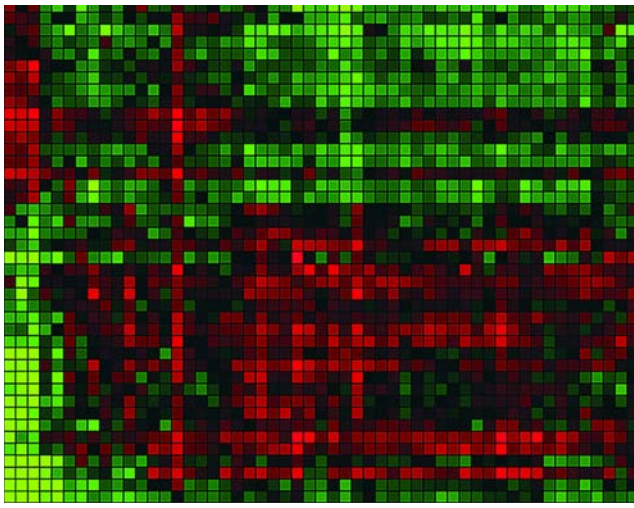

So-called "heat maps" like the one above show which genes are upregulated (red) and downregulated (green) during rejection of a transplanted heart.

PHASE 2: DEVELOPMENT OF A DIAGNOSTIC TOOL

Further analysis of the 252 candidate genes then narrowed the pool to a set of 62. During this phase, Dr. Deng and the study team worked with XDx to analyze each of these genes in patients who did and did not experience rejection to determine their levels

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Frontiers of Cardiovascular Medicine

Next generation hybrid: cardiothoracic surgeon as interventionalist.

Although interventional cardiology and cardiac surgery share the goal of repairing the heart and its vessels, the two have always been separate in practice and in training. Developed by cardiologists since the mid-1900's, interventional cardiology has traditionally been regarded as an extension of cardiology, while cardiac surgery is built upon training in general and specialized surgery.

Now, NewYork-Presbyterian Hospital is transcending the historic barrier between the disciplines by training cardiac surgeons in interventional procedures, providing combined therapeutic approaches, and conducting clinical studies and percutaneous device development.

Mathew Williams, MD

At NewYork-Presbyterian Hospital/Columbia University Medical Center, Mathew Williams, MD, established a joint one-year fellowship program and will be the first to complete it in December 2006. At NewYork-Presbyterian Hospital/Weill Cornell Medical Center, cardiothoracic surgeon Arash Salemi, MD, has incorporated endovascular treatment options into his cardiothoracic surgical practice after completing rigorous training in Europe.

Four days a week, Dr. Williams conducts interventional procedures at the NewYork-Presbyterian/Columbia catheterization suite under the supervision of interventional cardiologists Martin B. Leon, MD, Jeffrey W. Moses, MD, and others. "Mat's training is intensive," says Dr. Leon. "It's an advanced fellowship. He's on call. He does the clinical research-related work. He's doing academic projects. In his first four months he's already acquired very substantial skills, and in time he'll become a unique specialist who can simultaneously negotiate both cardiac catheterization and cardiac surgery very constructively and collegially."

"A cardiac surgeon's mastery of the discipline can represent a distinct advantage for patients," says Dr. Williams. Although it may appear that interventional cardiology and cardiac surgery are in competition, they are only broadening options for patients with heart disease. "Through my previous training in cardiac surgery I could evaluate patients and determine whether they were appropriate surgical candidates, but I could not necessarily comment on whether they were appropriate for stents," he says. "My training in interventional cardiology is giving me the skills to treat coronary and other cardiovascular conditions through the range of available treatments."

With the support of Weill Medical College of Cornell University faculty O. Wayne Isom, MD, Cardiothoracic Department Chair, and Karl H. Krieger, MD, Cardiothoracic Department Vice-Chair, Dr. Salemi spent four months training at the University of Paris and four months at San Rafael University in Milan. Both institutions are prominent in the endovascular and cardiovascular surgical community, and were able to provide training that was not readily available in the U.S. at the time he began. Since his return to NewYork-Presbyterian/Weill Cornell in February 2006, Dr. Salemi spends one day per week in the catheterization laboratory and four days in his surgery practice.

According to Dr. Krieger, "We believe the future of cardiac care will rest in the hands of cardiac specialists like Dr. Salemi who have hands-on experience in both disciplines. With training in both cardiac surgery and cardiology, they will be in the best position to guide our research into new areas that will result in improved patient care."

Dr. Salemi feels fortunate to have been able to receive this unique training and to help provide a bridge between the two disciplines at the hospital. "NewYork-Presbyterian/Weill Cornell has been very forward-thinking about providing new therapeutic modalities to our patients, in developing clinical algorithms, and in participating at the regulatory level with new technologies," he says. As co-investigator in the Evalve trial with Principal Investigator S. Chiu Wong, MD, Dr. Salemi refers many elderly patients with symptomatic congestive heart failure for evaluation for percutaneous mitral valve repair. "Having these percutaneous technologies available certainly presents opportunities for patients who are not eligible for open surgery," Dr. Salemi says.

CONTINUED ON P.5

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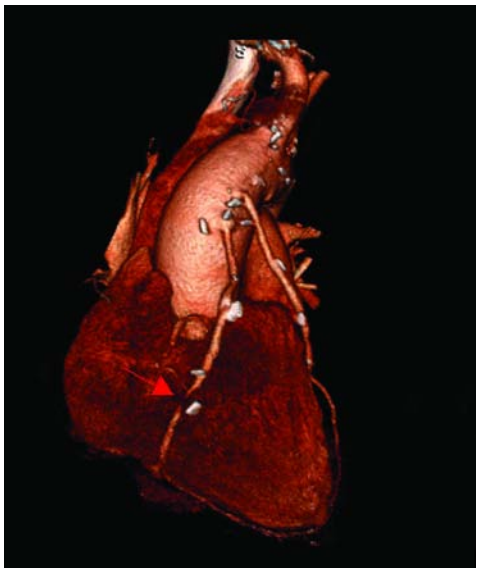
Improving Vein Graft Arterialization

Research on spironolactone could give an old drug a new indication for venous coronary artery bypass grafting.

Can an old dog learn new tricks, as the saying goes? A study led by Daniel F. Catanzaro, PhD, is investigating the use of spironolactone (aldactone) for a new application: reducing the extent of remodeling in vein grafts.

Approximately 400,000 patients undergo coronary artery bypass grafting each year in the U.S. While the majority of vein grafts are initially successful, occlusion of vein grafts limits their long-term success. Research shows that after ten years, only 60% of vein grafts remain patent.

In 1999, the Randomized Aldactone Evaluation Study (RALES) showed that when added to a regimen of other drugs administered to patients with congestive heart failure, aldactone significantly improved outcomes in many patients (reducing the risk of death by about 30% overall).



Three-dimensional rendering of CT angiograms show high grade stenosis of a saphenous vein graft to the right coronary artery.

Having long studied the molecular biology of the renin-angiotensin-aldosterone-system (RAS), Dr. Catanzaro speculated that the antifibrotic effects of aldactone might reduce the extent of remodeling during adaptive vein graft arterialization. The RAS plays a key role in maintaining normal blood pressure through its effects on vascular tone and electrolyte metabolism.

In collaboration with Principal Investigator Jeffrey Borer, MD, and Co-investigator Arash Salemi, MD, Dr. Catanzaro developed a clinical protocol to investigate whether the effects of aldactone could be harnessed to reduce venous occlusion after coronary artery bypass grafting (CABG).

During the first phase of study, the researchers performed carotid interposition grafting in pig models. In the subjects that received treatment with low-dose spironolactone, the outcome of the grafts was dramatically improved: diameter of the lumen was twice that in the control animals. Dr. Catanzaro acknowledges that because they used jugular veins that have thinner walls and therefore tend to balloon more than other vessels, the effects observed in the study may have been somewhat exaggerated. But the effect was clearly "huge" nonetheless.

Yet contrary to the researchers' expectations, the improvement was not due to reduced hyperplasia. "The drug seemed to dilate the artery so that when it remodeled, it remodeled around a dilated lumen," Dr. Catanzaro describes. The precise mechanism for this effect is unknown. "It may cause vasodilation either by enhancing nitric oxide bioavailability or, as some preliminary research suggests, it could block calcium channels directly."

Having established the beneficial effect of aldactone in animal models, the next step will be to determine whether the drug improves vein graft arterialization in humans.

"If it works the same way in people that it does in animals, this would help a lot of people," says Dr. Catanzaro. "Spironolactone has been used for decades, and is inexpensive." Its main use is diuretic, leading to sodium and water excretion. "But it may not be used to its full potential because it takes time to have effect in the body, and it has not been well understood how to best use it," he comments.

A secondary aim of the study is to investigate the possibility of establishing CT angiography as a new standard by which to assess outcomes after CABG. Dr. Catanzaro explains that today, CABG is considered successful if a patient's symptoms are alleviated. "Very few patients want to return to the hospital for angiograms to prove that their vessels are clear. But CT angiography may be able to provide definitive imaging of the vessels and be used as an objective measure of the operation's success. If this proves to be a reliable method, the noninvasive test could potentially replace invasive angiogram in determining who needs CABG. It could also provide a valuable way to measure whether or not procedures are successful."

During the next phase of study, patients at NewYork-Presbyterian Hospital and the Methodist Hospital in Houston will be randomized to either a control or spironolactone group. CT angiography will be performed 30 days after CABG, to determine its efficacy in viewing graft patency, vessel dimensions, as well as other indicators.

At the time of press, this study is pending Institutional Review Board (IRB) approval at NewYork-Presbyterian Hospital. Upon its completion, this phase of the study may establish new parameters upon which future study of vein graft arterialization can be conducted in large scale clinical studies. ■

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Alcohol Septal Ablation

New treatment provides less invasive, patient-friendly treatment of hypertrophic obstructive cardiomyopathy.

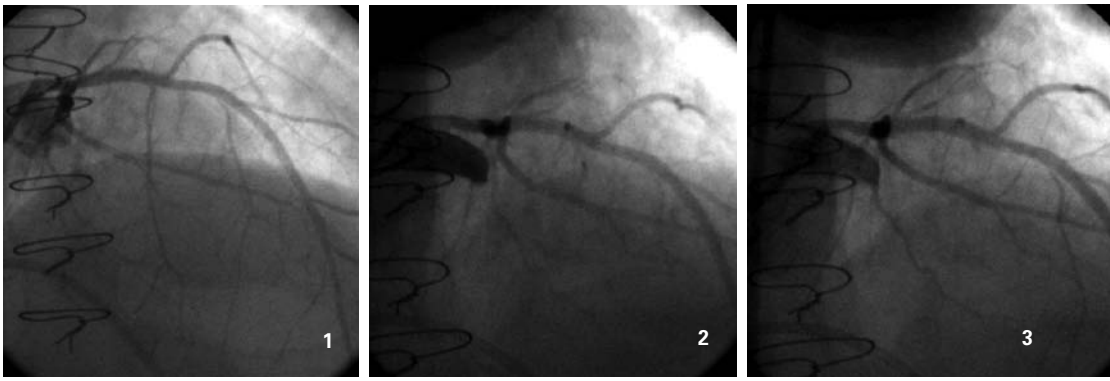
About one in 500 Americans has hypertrophic cardiomyopathy (HCM), the most common genetic cardiovascular disease. Up to half of patients have symptoms that inhibit their quality of life, the most severe being those with obstructed blood flow caused by severe thickening of the septal tissue (occurring in approximately 30% of all patients with HCM). If debilitating symptoms continue despite medical therapy, this subset may become a candidate for treatment by open-heart surgical myectomy or percutaneous alcohol septal ablation (ASA).

Until recently, many people with HCM have opted to live with discomfort and functional limitations, and a compromised quality of life, rather than undergo the rigors and risks of open heart surgery. "But patients are increasingly seeking treatment by ASA because of its similar efficacy and lower morbidity," says Srihari S. Naidu, MD, Assistant Professor of Medicine at Weill Medical College of Cornell University.

Alcohol septal ablation was first performed in 1994 by British physician Ulrich Sigwart, MD, who used angioplasty equipment to deliver alcohol into the patient's artery. In the decade since, the procedure has evolved to the point where it is likely performed more often than surgical myectomy worldwide. According to Dr. Naidu, who has facilitated the evolution of ASA with peer-reviewed publications detailing alterations in technique, the procedure offers patients a much less invasive, easier option than surgical myectomy. "This is reflected in the fact that more and more patients who have refused surgery are willing to consider and undergo alcohol septal ablation," explains Dr. Naidu.

ASA is performed during cardiac catheterization: the interventional cardiologist instills a small amount of alcohol directly and selectively into the septum, causing a targeted infarction. The infarction destroys a strategic area of tissue so it no longer contracts, thereby lessening the obstruction of blood flow from the heart. Over time, the dead tissue shrinks and the septum reduces in size in most patients, resulting in continued improvement over one to three years. The procedure takes about one hour, during which time patients are fully awake. A reduction in obstruction is typically noted immediately, according to Dr. Naidu.

ASA is suitable for patients whose quality of life is limited by symptoms such as chest pain, shortness of breath, palpitations, and syncope. Most of Dr. Naidu's patients are middle-aged individuals who want to maintain an active and productive lifestyle. Candidates must have suitable anatomy as well, so that alcohol can be directed through blood vessels to the appropriate area. As such, all patients require an echocardiogram and diagnostic cardiac catheterization. Dr. Naidu estimates that about four out of five of his patients have acceptable coronary anatomy for ASA to be effective.



1: Pre-ablation (septal artery visible) 2: Ablation (balloon in septal artery) 3: Post-ablation (septal artery no longer visible).

Risks of ASA include a national 5% risk of requiring a pacemaker, although none of Dr. Naidu's patients at NewYork-Presbyterian/Weill Cornell has needed one to date. Other known risks, such as access site bleeding and inappropriately large infarction, have also not been seen in Dr. Naidu's experience. Annual risk of sudden death in patients with HCM appears to be 1%, whether or not they undergo the procedure.

Five-year data show that ASA reduces symptoms in 90% of patients, which is equivalent to the success rate achieved with myectomy. "If ASA is insufficient, a patient could still go on to have surgery, and vice versa," says Dr. Naidu. With open surgery, however, patients can expect a three to four week recovery, time on a ventilator, and the discomforts and risks associated with open surgery. If patients go on to develop coronary disease and require surgery in later years, it is to their advantage to avoid open surgery beforehand.

Because HCM is a genetic disease, neither ASA nor surgery affects the underlying disease process, and some patients may

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Alcohol Septal Ablation CONTINUED FROM P.4

experience re-thickening of their septal tissue. Repeat procedures are occasionally needed. Nevertheless, thickening of the septum does not typically recur in most patients after surgery, and as far as data are available, after ASA.

Relatively few centers perform surgery or ASA for HCM on a routine basis today. To meet the need for comprehensive treatment of HCM, Dr. Naidu has established a special clinic at NewYork-Presbyterian/Weill Cornell, which provides initial consultations, catheterization and electrophysiologic therapies, and evaluation for medical, percutaneous, and/or surgical treatment. ■

Frontiers of Cardiovascular Medicine CONTINUED FROM P.2

There will always be a role for the people who do solely cardiac surgery and for those who do solely interventional cardiology, says Dr. Williams. "Some patients clearly need only a stent and some patients clearly need a surgical valve replacement," he says, "But there are also patients who may benefit from combined therapy. For example, if a patient needs a surgical mitral valve repair and also has significant coronary disease, a surgeon may decide on a traditional sternotomy (cutting of the breast bone) to perform the valve repair and a bypass surgery. But another option might be a combined approach, performing a minimally invasive mitral valve repair through a small incision in the chest wall and fixing the coronary arteries by inserting stents percutaneously. In situations like this, it would ideal to be trained in both surgical and interventional techniques."

Instituting a new fellowship and gaining its acceptance in the cardiology and cardiac surgery communities not only shifts the balance in clinical care, but represents a paradigm shift in medical education. To launch the fellowship at NewYork-Presbyterian/Columbia, Dr. Williams approached senior faculty at NewYork-Presbyterian/Columbia's cardiac surgery and cardiology departments. His mentors in cardiac surgery, Craig R. Smith, MD, Chief, Division of Cardiothoracic Surgery, and Mehmet C. Oz, MD, Clinical Vice Chair of Cardiovascular Services, were enthusiastic about the idea. This fellowship represents "a great opportunity," says Dr. Oz, "because the future of medicine is not so much within specialties but in the collaboration between them." The idea for the fellowship was also received enthusiastically in the Department of Cardiology, where interventional cardiologists have already been working together to develop new procedures with cardiac surgeons.

The fellowship will give Dr. Williams complete training in the techniques of interventional cardiology. His future practice will require a joint appointment in the Departments of Medicine and Surgery as well as hospital privileges in both the operating rooms and catheterization laboratories. The accomplishment evidently gives him a great deal of professional satisfaction and enthusiasm: "It's no longer about disciplines," he says. "It's about repairing the heart. And this puts everything else into perspective." ■

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Genomics-Based Test Replaces Heart Biopsy

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of activity. From there, further analysis produced an 11-gene set of the most significant genes associated with the immune changes in organ rejection. Using these 11 genes and another nine for control, the company developed the AlloMap™ molecular expression test – a tiny chip with 20 genes used to evaluate a cardiac patient's blood sample.

PHASE 3: **VALIDATION**

During this phase, a prospective, blinded study of post-transplant patients was conducted to verify whether the 20-gene test could accurately detect the absence of organ rejection.

Results: The test was able to consistently detect the absence of rejection. Patients with low scores had a very low risk of rejection, while those with higher scores were more likely to experience moderate to severe rejection.

As a result of this clinical trial, AlloMap™ testing for rejection after heart transplantation has been certified in all 50 states and is now covered by insurance. "This represents a paradigm shift in how transplant rejection will be monitored," Dr. Deng states. "For many patients, this simple blood test can now be used instead of invasive biopsy." Results of the CARGO study were published in 2006 in the *American Journal of Transplantation*. ■

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NewYork-Presbyterian Heart is comprised of physicians of Columbia University College of Physicians and Surgeons and Weill Medical College of Cornell University representing medical and surgical disciplines working together with other health professionals in a collaborative process.

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Faculty Highlights

James K. Min, MD, *Assistant Professor of Medicine, Weill Medical College of Cornell University, and Assistant Attending Physician at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.*

James K. Min, MD, was recruited to direct NewYork-Presbyterian/Weill Cornell's CT angiography (CTA) services for the diagnosis of coronary heart disease. He uses 64-slice CTA to accurately study coronary artery blockages in a non-invasive manner. As the Principal Investigator of several multi-center studies, Dr. Min is attempting to expand the use of CTA to include stress testing, and he is working to demonstrate the prognostic value of the technique.

Dr. Min joined the faculty of NewYork-Presbyterian/Weill Cornell in July 2005 after completing his medical degree at Temple University and his internship, residency, and fellowship at the University of Chicago.

Recent publications include "Prediction of Coronary Heart Disease by Erectile Dysfunction in Men Referred for Nuclear Stress Testing," *Arch Intern Med.* 2006;166:201-206, and "Indications for Coronary and Cardiac CT Angiography," *Cardiology in Review* (in press).

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During his 30-year tenure at NewYork-Presbyterian Hospital/Columbia University Medical Center, Dr. Spotnitz's research endeavors have centered on the effects of surgery on cardiac function. He was instrumental in inventing quantitative techniques for using intraoperative cardiography to measure changes in systolic and diastolic properties, and in applying that information to improve the surgical care of his patients. Clinically, Dr. Spotnitz has specialized in arrhythmia surgery. He developed new ablation techniques for patients with Wolff-Parkinson-White syndrome and ventricular tachycardia, and more recently developed transvenous insertion of pacemakers and defibrillators, with a special interest in application for infants and children.

Dr. Spotnitz has authored numerous publications, including "Ventricular diastolic stiffness predicts perioperative morbidity and duration of pleural effusions after the Fontan operation." *Circulation.* 2006 Jul 4;114(1 Suppl):I56-61, and "Left ventricular pacing site-timing optimization during biventricular pacing using a multielectrode patch." *Ann. Th. Surg.* (in press).

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