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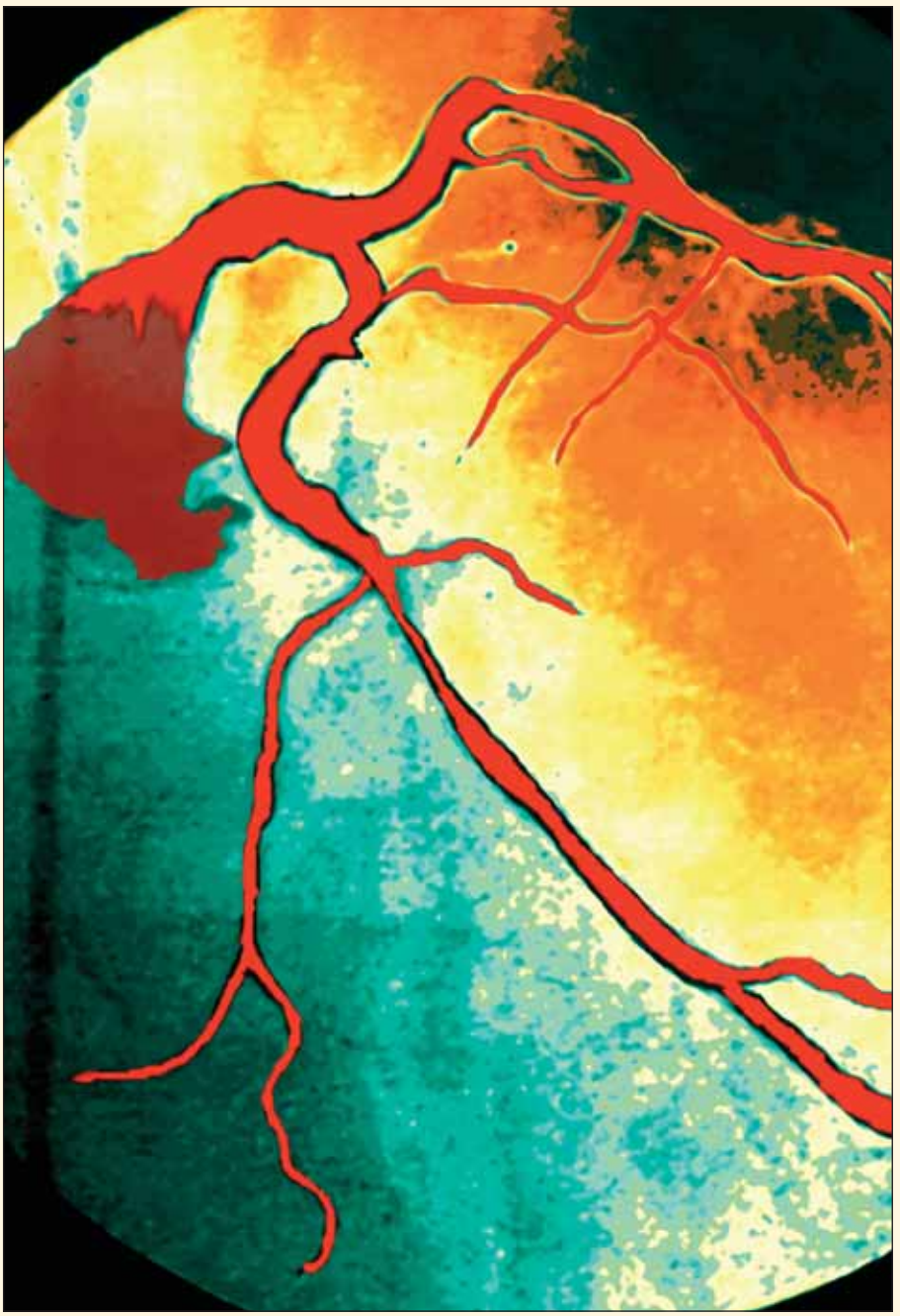

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MESSAGE FROM THE EDITOR

Welcome to the inaugural issue of the *Journal of the Methodist DeBakey Heart Center*, a quarterly source of information that will be both interesting and useful for cardiovascular physicians and research scientists.

The Methodist DeBakey Heart Center provides a forum for clinical and academic faculty in diverse disciplines to interact in such a way as to encourage optimal patient care, research and education. Similarly, this quarterly periodical will chronicle the highlights of cardiovascular research projects in the Heart Center, as well as clinical case studies and physician vignettes, with each article designed to educate and stimulate thought.

A broad spectrum of information will emphasize basic biomedical research in cell development, cardiovascular genomics, clinical and translational research, as well as clinical care. Evidence-based methods that improve health care, including patient outcomes and physician satisfaction, will be described.

Look also for historical notes related to current cardiovascular medicine, editorials on a variety of topics, letters-to-the-editor, perplexing clinical cases, and controversial opinions. We will strive for a publication that you will relish — the style concise and the content provocative enough to pique curiosities and provoke response.

The Journal will document the work of Methodist DeBakey Heart Center physicians, who are among the premier leaders in cardiovascular medicine. To that end, we plan to produce an exemplary periodical that will be visually attractive, readable and responsive to the needs of our audience.

This publication and this issue in particular are dedicated to Dr. Michael E. DeBakey, an inspirational leader in cardiovascular care for more than 55 years, and father of the Methodist DeBakey Heart Center. Today Dr. DeBakey remains actively engaged in his life's work, to the delight and advantage of us all. In this inaugural issue, he offers some of his unique insight. We deeply appreciate his enthusiastic support.

So please read, enjoy, and react. We welcome your comments. Inquiries and letters to the editor can be directed to jmdhc@tmh.tmc.edu.

Respectfully yours,

William L. Winters, Jr., MD
Editor-in-Chief
Journal of the Methodist DeBakey Heart Center

JOURNAL OF THE METHODIST DEBAKEY HEART CENTER
VOLUME 1, NUMBER 1

JMDHC provides an update from Methodist DeBakey Heart Center specialists about leading edge research, diagnosis and treatment.

U.S. News & World Report ranks the Methodist DeBakey Heart Center's cardiology, cardiothoracic and vascular surgery programs number 17 in the nation.

JMDHC is written for physicians, and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered, and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure or treatment for a given patient.

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THE CENTERS OF EXCELLENCE CONCEPT

Michael E. DeBakey

The inauguration of the *Journal of the Methodist DeBakey Heart Center* deserves high praise, and Dr. William Winters deserves our commendation for initiating this effort. I am deeply appreciative of his kindness in dedicating this inaugural issue to me and in inviting me to submit a statement.

The Methodist DeBakey Heart Center has a long and prolific legacy as a Cardiovascular Research Center extending over four decades. In 1960, I had the opportunity to present the Center concept to U.S. Senator Lister Hill, who was then Chairman of both the U.S. Senate Legislative and Appropriations Committees concerned with health. He asked me how I would define a cardiovascular center. The definition I gave him, I believe, still applies, and it may be appropriate to quote it:

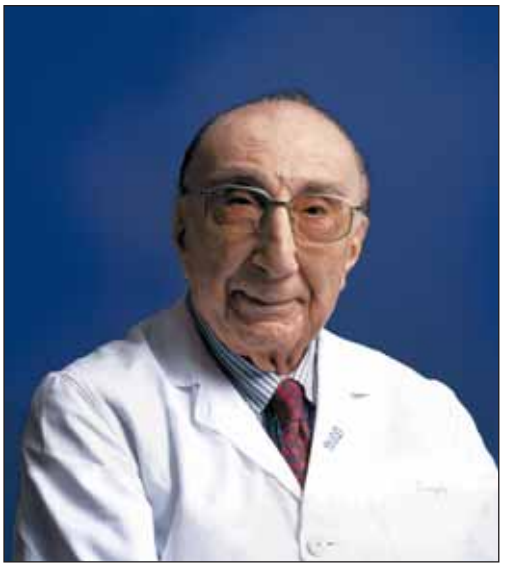
A Cardiovascular Research and Training Center is an organizational unit established for the specific purpose of advancing knowledge and developing the most effective techniques and methods for the clinical management and prevention of cardiovascular disease through research, teaching, and patient care.

Strongly oriented toward the problem of human disease, with the primary focus on the patient, the Center should be provided with all the resources, facilities and personnel essential to modern biomedical research and the conduct of the most sophisticated diagnostic and therapeutic procedures. Since the Center will be concerned with the total spectrum of cardiovascular disease problems, whose solutions will require the collaborative skills and talents of scientists from the various disciplines, it must be staffed by a corps of scientists representing the biological, engineering, physical, and social sciences, as well as the clinical disciplines.

The Center should be housed in a discrete geographic area to permit staff members to work in sufficiently close proximity with one another, and with sufficient integration of their activities, in order that ideas and technical advances can be continuously exchanged and critically evaluated and research opportunities immediately recognized and exploited. The Center provides for the most effective interface between the fundamental sciences and clinical investigation, and thereby permits the rapid advancement and application of knowledge derived from the various scientific disciplines toward the solution of cardiovascular problems. The Center should provide for the most favorable environment for attracting high-quality trainees in a wide spectrum of clinical and fundamental scientific disciplines, and for training and equipping them with the most advanced skills and techniques of current biomedical research and clinical cardiovascular investigations.

As incorporated in this definition, there is a need for continuous interchange and rapid diffusion of information and knowledge gained from the research endeavors of the different clinical and basic scientific disciplines. This is best achieved by regularly scheduled scientific meetings and publications. The latter can be well served by the new quarterly *Journal of the Methodist DeBakey Heart Center*. As Lord Chesterfield stated in one of his letters to his son in 1789:

"Next to doing things that deserve to be written, there is nothing that gets a man more credit, or gives him more pleasure, than to write things that deserve to be read."



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CENTER FOR CARDIOVASCULAR DISEASE PREVENTION: RISK ASSESSMENT AND REDUCTION

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INTRODUCTION

Cardiovascular disease is the number one cause of death in the United States, accounting for more than 1.4 million deaths each year (American Heart Association. Heart and Stroke Statistics—2004 Update. Dallas, Texas: American Heart Association, 2003). The Center for Cardiovascular Disease Prevention (CCDP) was created in 2000, as a partnership between the Methodist DeBakey Heart Center and Baylor College of Medicine, to identify and implement new preventive and therapeutic strategies to reduce pain, suffering and death from cardiovascular disease. In clinical and translational research, investigators at the CCDP use a comprehensive approach directed at improving both risk assessment and risk reduction.

IMPROVING RISK ASSESSMENT

Because many individuals who develop cardiovascular disease do not have traditional risk factors such as elevated low-density lipoprotein cholesterol (LDL-C), research has increasingly focused on additional factors that may refine risk assessment, to identify high-risk patients before they have a cardiovascular event. In particular, the importance of inflammation in both atherogenesis and atherothrombosis has led to the investigation of inflammatory mediators as markers of risk. A recent study conducted at the CCDP examined the relationship between lipoprotein-associated phospholipase A_2 (Lp-PLA_2)—a proinflammatory enzyme secreted by macrophages—and incident coronary heart disease (CHD) in middle-aged Americans.[1]

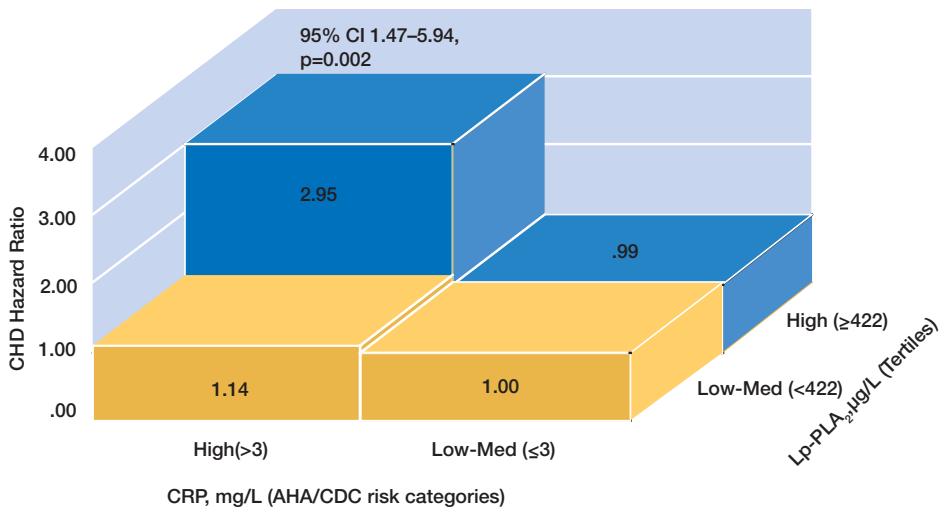

Figure 1.
Association of lipoprotein-associated phospholipase A2 (Lp-PLA_2), C-reactive protein (CRP), and risk for incident coronary heart disease (CHD) among individuals with low-density lipoprotein cholesterol (LDL-C) <130 mg/dL in the Atherosclerosis Risk in Communities Study. Reprinted with permission from Ballantyne CM et al. Circulation 2004;109:837–842.[1]

In this examination of participants in the Atherosclerosis Risk in Communities (ARIC) study, Lp-PLA_2 levels were higher in individuals who developed incident CHD. Among individuals with low LDL-C (<130 mg/dL, the study median), Lp-PLA_2 levels were independently associated with incident CHD, even after adjustment for traditional risk factors and C-reactive protein (CRP), an inflammatory marker previously shown to be an independent predictor of CHD. Also, among individuals with low LDL-C, high levels of both Lp-PLA_2 and CRP indicated the greatest risk for CHD—almost three times that of individuals with low to medium levels of both inflammatory markers (Figure 1).[1]

IMPROVING RISK REDUCTION

While the benefit of lipid-modifying therapy on cardiovascular disease prevention has been established in multiple large clinical trials, in practice, many patients do not achieve the LDL-C recommendations of the National Cholesterol Education Program Adult Treatment Panel III (ATP III).[2] Researchers at the CCDP continue to lead clinical investigations that evaluate the effectiveness

of new lipid-modifying therapies.

Statins are first-line therapy for reducing LDL-C in most patients. The newest statin, rosuvastatin, was compared with atorvastatin, simvastatin and pravastatin in the multicenter Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial. Rosuvastatin was found to provide significantly greater reductions in LDL-C than the other statins (Figure 2) and to enable more patients to achieve LDL-C goals.[3]

Although the primary effect of statins is to lower LDL-C levels, statins also have been shown to reduce levels of CRP. In the multicenter Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial,[4] which is ongoing at the CCDP, individuals with low LDL-C (<130 mg/dL) and elevated CRP (≥2 mg/L) are randomized to receive rosuvastatin (20 mg/day) or placebo. Patients will be followed up for 3.5 years to assess the effect of rosuvastatin on risk for a first cardiovascular event. Although patients in the JUPITER trial would not be considered for drug therapy by the ATP III guidelines, they may be at increased risk because of a heightened inflammatory response. The results of this ongoing investigation should help clarify mechanisms by which statin therapy reduces cardiovascular risk across a range of LDL-C levels, including levels not considered elevated by the current guidelines.

The LDL-C–lowering effectiveness of statins may be limited not only by drug efficacy but also by concerns about the safety of high-dose therapy. Combination therapy using agents with complementary mechanisms of action may provide a safer option. Combining a statin, which inhibits cholesterol synthesis in the liver, with a cholesterol absorption inhibitor, which inhibits cholesterol absorption in the intestine, may enable more patients to safely achieve optimal LDL-C levels for CHD risk reduction.

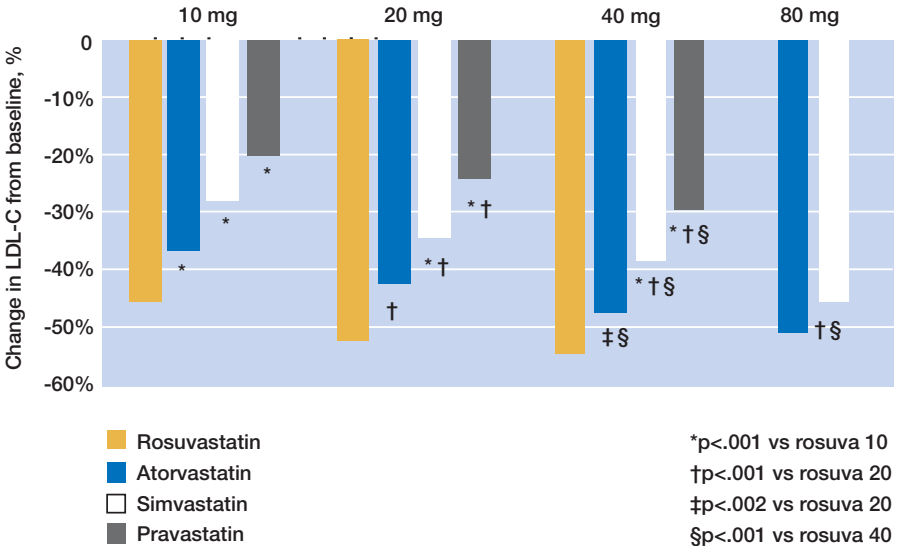

Figure 2.
Comparative LDL-C–lowering efficacy of statins in the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial.[3]

In a recent study conducted at the CCDP, atorvastatin monotherapy was compared with the combination of atorvastatin and the cholesterol absorption inhibitor ezetimibe across a range of atorvastatin doses in patients with hypercholesterolemia.[5] Depending on atorvastatin dose, ezetimibe plus atorvastatin provided LDL-C reductions of 50–60% (Figure 3), and in an analysis that pooled all atorvastatin doses, coadministration of atorvastatin and ezetimibe provided an additional 12% reduction in LDL-C compared with atorvastatin alone. Further, combination therapy of ezetimibe plus atorvastatin at its lowest dose (10 mg) provided similar LDL-C reduction to maximum-dose atorvastatin monotherapy (80 mg): 50% and 51%, respectively.[5] Combination therapy with ezetimibe and a statin therefore offers a new treatment option to achieve recommended LDL-C goals.

While lowering LDL-C has been shown to slow or even stop atherosclerotic progression, raising high-density lipoprotein cholesterol (HDL-C) may actually reverse the disease progress.[6] The cholesteryl ester transport protein (CETP) inhibitor torcetrapib has been shown to increase HDL-C levels by 15–90%;[7] by comparison, statins usually increase HDL-C by only 5–10%. In ongoing studies at the CCDP, the potential benefit of combining LDL-C–lowering statin therapy with HDL-C–raising torcetrapib is being examined in two high-risk populations: patients with mixed dyslipidemia and those with a family history of CHD, total cholesterol ≥300 mg/dL, and LDL-C >200 mg/dL. Patients are randomized to receive atorvastatin plus torcetrapib or atorvastatin plus placebo and monitored by carotid ultrasound to measure change in intima–media thickness.

Other agents under development that are being studied at

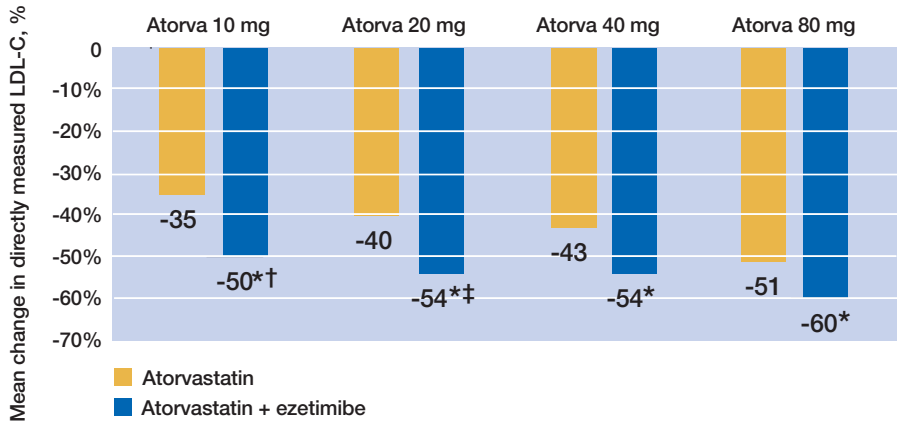

Figure 3.

Effect of combination therapy with ezetimibe and atorvastatin compared with atorvastatin monotherapy on directly measured LDL-C.[5] Reprinted with permission from Ballantyne CM et al. Circulation 2003;107:2409–2415.

the CCDP include an acyl-CoA: cholesterol acyltransferase (ACAT) inhibitor, which is being studied in patients with heterozygous familial hypercholesterolemia to determine whether it will reduce progression of carotid atherosclerosis as assessed by ultrasound. In addition, an immunomodulatory approach to cardiovascular disease prevention, using a procedure that targets the underlying chronic inflammation involved in atherosclerosis, is being studied in patients with peripheral arterial disease.

Imaging modalities provide noninvasive assessment of therapeutic efficacy. Investigators at the CCDP have begun a large National Institutes of Health (NIH) trial, in collaboration with the Section of Vascular Surgery of Baylor College of Medicine, to determine whether triple therapy with a statin, ezetimibe, and niacin can stop or reverse atherosclerosis. The Effect of Lipid Modification on Peripheral Arterial Disease after Intervention Trial (ELIMIT) will test the hypothesis that additional reductions in atherogenic lipoproteins and increases in HDL-C with combination therapy will stop or even regress atherosclerosis more effectively than statin monotherapy. Patients with peripheral arterial disease will be randomized to receive either simvastatin 40 mg monotherapy or triple therapy with simvastatin 40 mg, extended-release niacin 1500 mg and ezetimibe 10 mg. The primary endpoint of peripheral arterial disease progression will be assessed by magnetic resonance imaging (MRI); secondary endpoints include walking time, ankle–brachial index, clinical events, and inflammatory and thrombotic markers.

RESEARCH OPPORTUNITIES

With more than 20 ongoing clinical trials, the Center for Cardiovascular Disease Prevention is currently recruiting patients with high cholesterol, high triglycerides, mixed hyperlipidemia, metabolic syndrome, diabetes or peripheral arterial disease. To refer a patient for a study, please call 713-798-3171 or 713-798-3330.

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STENT GRAFT REPAIR OF ABDOMINAL AORTIC ANEURYSM

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INTRODUCTION

The aortic stent graft currently represents a pinnacle in the evolution of endovascular technology - beginning with the DeBakey Dacron, vascular graft (which remains a gold standard), through catheter-based approaches to vascular disease, culminating in the introduction of the endovascular stent by Palmaz in 1985.[1] Subsequently, while searching for a minimally invasive treatment for patients with abdominal aortic aneurysm (AAA) that are too sick for open surgery, Juan Parodi (1991) was the first to combine the Dacron graft with a Palmaz stent.[2] Parodi sewed Palmaz stents onto the graft, crimped the entire device onto an angioplasty balloon, and became the first to deliver an endoluminal graft into the aorta. By excluding the aneurysm internally, reducing pressure on the aortic wall, and preventing rupture, the repair of aortic aneurysms was changed forever. Since it is unusual for aneurysms to be confined to the aorta alone, bifurcated grafts, which extend into the common iliac arteries, were a natural extension of this technology.[3] Parodi's pioneering work led to the development of the first commercially available stent grafts in 1997, the Medtronic Aneuryx graft[4] and the Guidant Ancure graft.[5,6] Today there are three commercially available grafts in the United States, with another five in development.[7]

Aneurysms of the abdominal aorta are typically repaired when they are greater than 5 cm in diameter. However, there is increasing evidence that the decision to intervene should be based on the size of the aneurysm relative to the patient's native aortic diameter.[8-10] For example, a small woman with a 5 cm AAA may be at a proportionately higher risk for rupture than a male with an equivalent sized aneurysm. Also, because most AAAs are asymptomatic, with rupture being the most frequent presenting symptom, there is increasing interest in ultrasound-based screening programs to permit early detection and intervention.[11,12]

TECHNICAL ASPECTS OF ENDOLUMINAL GRAFTS

Endoluminal grafts represent a radical change in the approach to prevention of aneurysm rupture. Instead of opening the aneurysm and sewing a graft into the aorta, endografting requires that blood be routed through the endoluminal graft, a seal be made at the top and bottom of the aneurysm, and the distending arterial pressure be minimized. The endoluminal graft must essentially have secure fixation and adequate sealing at the attachment zones above and below the aneurysm (in the aorta and iliac arteries). Fixation and sealing have been achieved by a combination of hooks, stent rings with hoop strength (outward force), suprarenal stent attachment and sealing rings.[3,13,14]

OPEN VERSUS ENDOVASCULAR REPAIR

It has been greatly debated in the surgical community whether endovascular grafting should be reserved only for high-risk patients or should be offered to all patients with suitable anatomy. Currently more than 50% of AAAs can be repaired using endovascular techniques, although some patients are better candidates than others.[15-17] However, in patients who are at extreme risk for an open operative repair, it is permissible to use an endograft, even with unfavorable anatomy.[17]

The controversy regarding open versus endovascular repair exists in part due to the increased costs associated with endovascular stenting and the lack of long-term follow-up data for this procedure.[18] At the present time, placement of an endograft for AAA is more expensive, primarily due to intensive imaging requirements during follow up. Although the device itself is more expensive than a Dacron graft ($12,000 vs. $700), initial hospital costs are generally similar due to the need for ICU care, longer length of stays (LOS), and increased respiratory complications associated with

AORTIC ANEURYSM FACTS

- 70% involve the common iliac arteries
- AAA grow on average 0.4 cm/year
- AAA are usually asymptomatic
- Most AAA present for years before incidental detection
- Risk of rupture is directly related to the AAA diameter
- Risk of rupture increases rapidly in aneurysms > 5 cms
- Most ruptured aneurysms are fatal
- Symptomatic aneurysms should be repaired expeditiously

ADVANTAGES OF ENDOLUMINAL GRAFTING

- Delivery through femoral artery possible with X-ray guidance
- General anesthesia can be avoided
- Blood loss is minimized
- ICU stay is not required, hospital stay is reduced
- Return to full function is much more rapid.

DISADVANTAGES OF ENDOLUMINAL GRAFTING

- No long term follow up (5-yr. data recently available)
- Remodeling may lead to re-pressurization
- Back pressure from lumbar arteries may cause aneurysm growth
- Routine CT follow up is mandatory
- Approximately 10% require catheter-based intervention in first 24 months

open surgery. In addition, preoperative evaluation of an aneurysm for endografting is more time consuming than for open AAA repair. The physician has to carefully evaluate the aortic anatomy to determine whether the patient is a suitable candidate. This is largely determined based on preoperative evaluation of the aneurysm anatomy through CT scanning. A virtual endograft, and new techniques for measuring aneurysms and following them post-implantation have been developed as a result of aortic endografting.[19]

Jordan et al.[15] reported their experience with both open and endovascular AAA repair in both low and high risk patients.[16] The authors concluded: "Both high-risk and low-risk patients can undergo endovascular repair with a lower rate of short-term systemic complications and a shorter LOS when compared to open AAA repair. While we do not have complete understanding regarding the long-term durability of these endovascular grafts, our delayed intervention, thus far, has been minimal. For that reason and due to the lower rate of early complications, high-risk patients should be preferentially considered for EVAR over open AAA repair. Considering that low-risk patients also had fewer complications, patients who are anatomically suitable may be offered EVAR with a varying degree of emphasis, depending on their physiologic risk, and with cautious consideration about the unknown long-term durability."[15]

Further, the authors noted that patients who underwent endografting had fewer complications and a shorter LOS. When complications do occur, there is less morbidity than with open AAA repair, and patients have fewer additional hospital days due to complications.[15] Future technical developments will permit an increasing number of patients to be treated with endovascular techniques.

The Methodist Hospital will soon begin a phase 2 clinical trial involving the first truly percutaneous endograft. The Trivascular device, which will be used during the investigation, has a very small profile permitting insertion via a 12 Fr sheath. For more information 800-336-3664.

COMPLICATIONS OF AORTIC ENDOGRAFTS

Endograft complications can occur during both insertion and follow-up procedures. During initial clinical trials, iliac artery injury occurred in up to 7% of cases due to the size of the devices and poor patient selection. However, as devices become smaller and more flexible, and with improved preoperative imaging, the incidence of injury has decreased. In less than 1% of cases thrombi associated with the aneurysm dislodge resulting in embolization to the lower extremities, kidneys or intestine. Groin complications related to the surgical exposure of the femoral arteries also occur due to infection, lymph leak and groin hematoma; however, these are rarely limb or life threatening. Delayed complications can also occur and are often due to aneurysm remodeling. When an aneurysm is excluded, it shrinks both in diameter and length. This can result in bending and dislodgement of the endograft with resultant pressurization of the endograft. This is called an "endoleak" as blood is entering the aneurysm. A high pressure or type 1 endoleak occurs when the graft has failed to seal at the aortic or iliac artery seal zones. This type of endoleak, which can lead to late rupture, must be detected and addressed. A type 2 endoleak, which is much more benign, occurs when flow in the lumbar arteries or inferior mesenteric artery reverses after the endograft is inserted and causes pressure to be applied to the AAA. Management of a type 2 endoleak is much more controversial, and in most cases can be observed in the absence of aneurysm growth.

FURTHER APPLICATIONS FOR STENT GRAFTS INCLUDING RUPTURED ANEURYSMS

Endovascular grafting is now being increasingly utilized in treatment of atherosclerotic occlusive disease, vascular trauma, and in dialysis access. Thoracic aortic endografting is being evaluated in prospective trials in the United

ENDOGRAFTS FOR RUPTURED AAA

- Permissive hypotension – do not aggressively restore blood pressure
- Place balloon in descending thoracic aorta via left brachial artery
- Emergent CT scan to size for endograft
- Emergent placement of endograft via femoral arteries

States with the potential to deliver even greater benefits than infrarenal AAA repair when compared to the open surgical procedure. Another very exciting development is the use of stent graft technology to reduce the extremely high mortality of the ruptured abdominal aortic aneurysm.

A ruptured aneurysm in a patient who survives to reach a hospital remains approximately 50%. This has not been impacted by improved anesthesia, surgical or ICU care. Recently, however, the vascular surgery group from Montefiore has reported that emergent endografting, with "permissive hypotension" until the endograft has been placed, resulted in a significant reduction in perioperative mortality.[20,21] These data have now been replicated at several major centers. This approach has challenged many of the concepts for treatment of ruptured AAA, long held by vascular surgeons. It is likely to become the standard of care.

FUTURE DEVELOPMENTS

- Branched vessel endografts permit treatment of aneurysms involving the renal arteries
- Biologic modifications encourage cell in growth into the graft
- Smaller more durable devices permit true percutaneous insertion
- External monitoring of endograft pressure
- Ultrasound screening programs for early detection of AAA
- Increasing use of emergent endografting for ruptured AAA

In summary, although we are early in the evolution of endograft development, this technology represents a major step forward in minimally invasive therapy for AAA, with particular advantage for patients at high risk for open AAA repair.

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Methodist DeBakey Heart Center Expands CME Offerings

BENCH TO BEDSIDE

SCIENCE CLINICAL TRIALS TREATMENT

The Heart Center is pleased to announce the launch of online accredited CME activities discussing ongoing research and clinical efforts. These activities are part of a growing series highlighting the Heart Center's bench-to-bedside approach to evidence-based medicine.

New Directions in the Treatment of Peripheral Arterial Disease

Alan B. Lumsden, MD; Christie Ballantyne, MD; Joel D. Morrisett, PhD; and Paul F. Bray, MD present key concepts and future directions in peripheral arterial disease (PAD), an emerging epidemic that is severely under diagnosed in the United States.

To access this activity, log on to www.methodisthealth.com/padj.

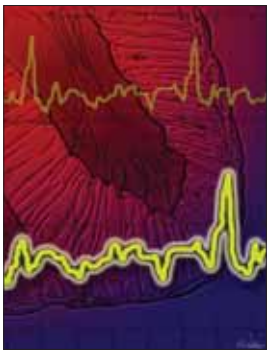
The Role of Inflammation in the Pathogenesis of Heart Failure

Christie Ballantyne, MD; Douglas Mann, MD; and Guillermo Torre-Amione, MD discuss immunological and molecular alterations that occur during heart failure, including the relevance of inflammation in disease progression.

To access this activity, log on to www.methodisthealth.com/chfg.

Upcoming Live CME at AHA Scientific Session

DIASTOLIC HEART FAILURE: *The Heart of the Matter*



Saturday, November 6, 2004
2:00 pm – 4:00 pm
Doubletree Hotel
International Ballroom
New Orleans, Louisiana

An expert panel will present information on current investigative theory, diagnosis and treatment of diastolic heart failure. The session will also introduce some of the new management therapies used by tertiary care heart failure centers to care for advanced, complex cases.

Faculty
William C. Little, MD
Wake Forest University School of Medicine
Douglas L. Mann, MD
Methodist DeBakey Heart Center,
Baylor College of Medicine
Miguel A. Quinones, MD
Methodist DeBakey Heart Center,
Baylor College of Medicine
Guillermo Torre-Amione, MD, PhD
Methodist DeBakey Heart Center,
Baylor College of Medicine

www.debakeyheartcenter.com/ahasymposium

Jointly Sponsored by Methodist DeBakey Heart Center and Baylor College of Medicine

New Academic Affiliation Formed

The Methodist Hospital recently announced the formation of a primary academic affiliation with Weill Cornell Medical College and New York Presbyterian Hospital. This 30-year agreement will draw on the strengths of all three internationally renowned institutions to enhance patient care, clinical and biomedical research, and medical education.

The alliance offers unique opportunities to foster new initiatives across the spectrum of academic medicine, including clinical trials, international medicine, national health care policy, outcomes research and graduate medical education.

With 1,269 beds, The Methodist Hospital is one of the largest acute care hospitals in the southwest, and one of the country's largest private not-for-profit hospitals. New York-Presbyterian Hospital, with 2,397 beds, is the largest hospital in the northeast, and the anchor of New York-Presbyterian Healthcare System. Weill Cornell Medical College is among the top ranked medical education, clinical and research centers in the United States with over $245 million in NIH-funded research grants.

U.S. News & World Report

The Methodist Hospital has been named among the country's top hospitals for heart and heart surgery in *U.S. News & World Report's* 2004 America's Best Hospitals issue. The hospital's Methodist DeBakey Heart Center currently is ranked 17th for its heart and heart surgery programs.

Methodist also is ranked among the country's top centers for neurology and neurosurgery; urology; ear, nose and throat; psychiatry; kidney disease; ophthalmology; gynecology; and orthopedics.

Ongoing Clinical Trials

The Methodist DeBakey Heart Center is dedicated to improving clinical outcomes through evidence-based medicine. Visit www.debakeyheartcenter.com to access information regarding ongoing clinical trials related to cardiovascular disease.

THE MICROMED DEBAKEY VAD®: A BRIDGE TO THE FUTURE

George P. Noon, David L. Joyce

From Methodist DeBakey Heart Center and Baylor College of Medicine, Houston, Texas

INTRODUCTION

Ventricular Assist Device (VAD) therapy has emerged as a promising new option for the treatment of end-stage heart failure. As a bridge to heart transplantation, pulsatile VAD implantation has been performed over 3,000 times worldwide with a success rate of 50-70%.[1,2] In the recent landmark REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial, end-stage heart failure patients, who received VAD but were ineligible for transplantation, were found to have a dramatic survival advantage over patients treated with optimal medical management (OMM).[3] On the basis of these results, VAD implantation is now indicated for destination therapy that may impact the care of thousands of patients. Despite the survival advantages associated with mechanical support, these patients are at risk for device-specific complications. The first generation pulsatile Left Ventricular Assist Devices (LVADs) were large, noisy, prone to failure and infection, and expensive (approximately $70,000 per device).[1] Recognizing these limitations, researchers began searching for alternative pump designs and axial flow impeller pumps emerged as the second generation of mechanical VAD. This article describes the development by Dr. George Noon, Dr. Michael E. DeBakey, and NASA engineers of the first axial flow pump for long-term cardiac support.

DEVELOPMENT OF THE AXIAL FLOW DESIGN

In 1984, a NASA-Johnson Space Center (JSC) engineer, David Saucier, underwent cardiac transplantation at The Methodist Hospital in Houston, TX. In 1988, we contacted him to set up a meeting with engineers at NASA who were working with axial flow pumps. Saucier expressed an interest in the ongoing artificial heart research at the Baylor College of Medicine and a collaboration was formed in which NASA spacecraft technology was applied toward the development of an improved VAD. This combined effort resulted in the development of a clinical axial flow pump that differed from existing pulsatile devices in its small size (86-mm long, 25-mm wide, and only 95 g), simplicity of design (only one moving part), and continuous flow characteristics (Figure 1).[4] The pump consisted of a titanium inflow cannula, a housing unit containing the impeller and motor, and a Vascutec gelweave vascular graft that served as an outflow graft for anastamosis with the ascending aorta.

During the development of the pump, initial in vitro studies revealed problems related to hemolysis.[5] On the basis of computational fluid dynamic analysis, a flow inducer was added to the front of the pump impeller in order to eliminate high negative pressure areas at the leading edge.[6] Polycarbonate replaced polyether polyurethane in construction of the pumps, after in vitro testing demonstrated thrombus formation on the flow straightener and

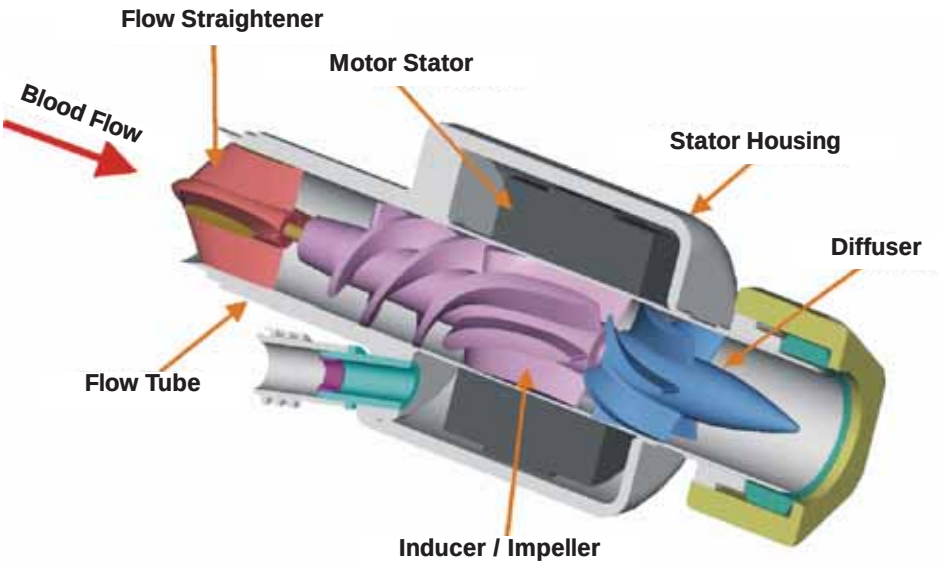


Figure 1. Internal components of the MicroMed DeBakey VAD®

Figure 2. External components of the MicroMed DeBakey VAD®

impeller of developmental models and a computer numerically controlled (CNC) fabrication process was adapted.[6] Taken together, these changes produced an index of hemolysis of 0.0029 +/- 0.0009 g/100 L, well within accepted limits.[6]

Following successful completion of in vitro testing, the MicroMed DeBakey VAD® was implanted in a paracorporeal position in eight animals. Although the initial ex vivo testing revealed problems with thrombus formation, minor design optimization and heparinization alleviated these problems.[7,8] The titanium VAD was then evaluated in 19 calves, demonstrating the safety and performance of the device for up to 145 days.[9] Thrombus formation, hemolysis and infection were minimal in these studies, and preparations were made for bringing this technology to clinical application.

The final pump design implemented for clinical use was capable of flows of 10 L/min against 100 mm Hg pressure with a speed of 12,500 rpm. A Clinical Data Acquisition System (CDAS) was used to monitor flow curves (via a flow probe positioned over the outflow graft), speed, current and power. An external battery pack was incorporated into the controller module to permit mobility and hospital discharge (Figure 2).

CLINICAL EXPERIENCE WITH THE DEBAKEY VAD

In November of 1998, the DeBakey VAD was clinically implanted for the first time in Europe.[10] The surgical procedure for implantation was similar to the one used for first-generation devices, with median sternotomy and initiation of cardiopulmonary bypass (CPB). An extrapericardial, subdiaphragmatic pocket was formed below the rectus muscle on the left side for positioning of the device. An apical fixation ring was sewn to the apex of the left ventricle, followed by insertion of the inflow cannula. The power and flow probe cables were externalized using a trocar via the right lower quadrant of the abdomen, and the outflow graft was anastamosed to the ascending aorta. Following deairing, pump flows were initiated at 7,500 rpm and adjusted for adequate pump index.[11,12]

The significance of these first clinical implants cannot be overstated, as this represented the first time that the human circulation had been supported long term by continuous flow (previous animal studies had suggested the feasibility of this strategy).[13,14] Interestingly, as clinical experience with the device progressed, clinicians began to observe near-physiologic pulsatile blood flow (as measured through Transcranial Doppler studies) in the setting of axial flow support.[15] Pulsatile flow was attributed to the contractions and pressure changes of the unloaded left ventricle and partially recovered right ventricle. The aortic valve often remained closed throughout the cardiac cycle early after implantation.[15] However, with some ventricular recovery it would begin to open.

To date, over 240 patients have been supported with the DeBakey VAD as a bridge to transplant, representing the greatest clinical experience for any axial flow pump. Device-related adverse events parallel those associated with first-generation pumps, with linearized rates (events/patient-year) of 2.03 for reoperation due to bleeding, 0.61 for hemolysis, 0.16 for device infection, 0.61 for thromboembolic event, 0.61 for pump thrombus, and 0.13 for pump failure (Table 1).[1] With a mean support time of 75±81 days, 45% of patients died on support while 55% in the European trial were successfully transplanted.[1] The combined FDA feasibility trial had a bridge to transplant success of 67%. These initial findings demonstrate the safety and effectiveness of axial flow as an alternative to pulsatile support.

FUTURE DIRECTIONS

After establishing the success of the device as a bridge to transplantation, MicroMed Technology, Inc. obtained approval from the Food and Drug Administration (FDA) for use of the VAD in a destination therapy clinical trial. The "DELTA" (Destination Evaluation Long-Term Assist) trial will randomize 360 patients in a 2:1 ratio for implantation of either a MicroMed DeBakey VAD or a Thoratec HeartMate XVE® device. An interim review will be performed following the first 152 implants. This trial represents a significant milestone in the development of a mechanical cure for heart failure in that it may open the door for rotary blood pumps as permanent therapy.

In addition to its potential role in destination therapy, a modification of the DeBakey VAD shows promise as a bridge to transplant in the pediatric population. Since the first successful use of a DeBakey VAD as a bridge to transplantation in a pediatric patient in 1990, mechanical circulatory support has gained increasing popularity in Europe for the treatment of children.[16] However, the low Body Surface Area (BSA) associated with this population represents an obvious limitation of implanted pulsatile VADs. For this reason, use of a miniaturized axial flow pump in this subset of patients may be an attractive new application for this technology. After humanitarian device exemption was obtained from the FDA for use of the DeBakey VAD, in children aged 5 to 16 awaiting heart transplantation, this device was implanted successfully in a 6-year-old girl with severe cardiomyopathy. This early experience raises hopes of using axial flow technology to improve outcomes in pediatric heart failure patients.

Nearly two decades after the concept of using an axial flow pump to support the human circulation was first visualized, the DeBakey VAD shows great promise as a treatment for end-stage heart failure. By departing from the traditional mentality that pulsatility was an essential requirement of a mechanical assist device, this pump represents an important bridge to the future of LVAD technology as a treatment for heart failure.

ADVERSE EVENT	INCIDENCE	RATE/PT-YEAR
Reoperation for bleeding	32.0% (48/150)	2.03
Hemolysis*	12.0% (18/150)	0.61
Device infection	3.3% (5/150)	0.16
Thromboembolic†	10.7% (16/150)	0.61
Pump thrombus	11.3% (17/150)	0.61
Mechanical failure	2.7% (4/150)	0.13

* defined as plasma free hemoglobin >40 mg/dL.

† composiste of embolic stroke, transiet ischemic attack, and peripheral embolism.

Table 1. Incidence and Linearized Rate of Adverse Events Following MicroMed DeBakey VAD® Placement.[1]

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MECHANICAL CIRCULATORY SUPPORT: RESPONSE OF THE FAILING HEART TO A NEW GENERATION OF PUMPS

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INTRODUCTION

Since the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) clinical trial demonstrated the superiority of long-term mechanical support for end-stage heart failure[2] patients have been offered ventricular assist devices (VAD) as a standard therapeutic bridge to cardiac transplantation.[1,4] However, expanding indications and greater utilization of mechanical circulatory support has led to the development of smaller and technically varied VADs. As opposed to the currently approved VADs, newer systems provide continuous non-pulsatile circulatory support using impellers in an axial flow system (Figure 1). The purpose of this review is to present the current status and applications of axial flow pumps, as well as to discuss the response of the failing myocardium to continuous flow support.

CONTINUOUS VERSUS PULSATILE CIRCULATORY SUPPORT

Mechanical support devices move blood from the left ventricle into the ascending aorta bypassing the aortic valve (Figure 2). Pulsatile pumps powerfully unload the ventricle and essentially replace the work of the heart, while maintaining peripheral pulses. In fact, it has been suggested that, over time, the myocardium may undergo atrophy, and the aortic valve develop significant calcifications and stenosis due to being persistently closed. These pulsatile VAD can be placed intra- or extra-corporeally, despite limitations to patient mobility. However, only external pumps are currently approved for right ventricular support. These devices are indicated for inability to wean from cardiopulmonary by-pass, and as a bridge to cardiac transplantation.[3] Patients supported with these devices typically remain hospitalized until definitive therapy is established.

Continuous flow systems may be technically easier to implant, are suitable for smaller patients and, while they are at an earlier stage of development, appear to be adequate alternatives to bridge patients to cardiac transplantation. When patients are fully supported with continuous flow devices, there is no variation in systolic-diastolic pressure and therefore, peripheral pulses are not detected. However, if the support of a continuous flow device is reduced to allow flow thorough the aortic valve, pulsatility can be maintained.

Long-term continuous flow pumps utilize turbine-like impellors aligned to receive blood in an axial fashion, and continuously eject blood into the aorta. At the present time, there are three implantable devices that provide continuous flow support. One of these devices, the MicroMed DeBakey VAD®, is currently approved in Europe as a bridge to cardiac transplantation, and in the United States for utilization in pediatric populations. It also is undergoing clinical evaluation in the United States in randomized clinical trials as a bridge for cardiac transplantation, as well as for destination therapy.

The primary advantage of continuous or axial flow pumps over pulsatile pumps is their smaller size, which makes them easier to implant, even in small patients. In addition, axial flow pumps are noiseless and may decrease the risk of device-associated infection.

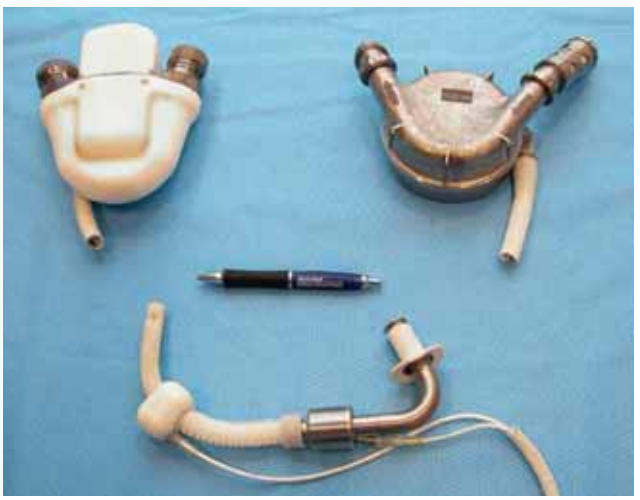

Figure 1. Left Ventricular Assist Device. The devices in this figure illustrate pulsatile (top two) and continuous-axial flow (bottom) pumps.

In addition to being placed in the ventricles of the heart, continuous flow devices also can be placed extra-corporeally. The external continuous flow devices are generally used for a short length of time, typically a few weeks, and are very helpful for patients who failed weaning from cardio-pulmonary bypass following cardiac surgery. These kinds of pumps can be placed to assist either the failing right or left ventricle.

One of the most recent and novel implantable axial flow pumps designed for short-term support is the Impella Recover System, which can be percutaneously placed via the femoral artery. This system offers full circulatory support to patients who are in cardiogenic shock without an open cardiac procedure. Physicians from the Methodist DeBakey Heart Center recently implanted the first system of this type in a patient in the United States. The effectiveness of its pumping ability was demonstrated by the dramatic decrease in left ventricular size that occurred following placement of the device. The Impella System is currently in clinical trials in five centers across the United States including the Methodist DeBakey Heart Center (Figure 3).

EFFECTS OF CONTINUOUS, AXIAL FLOW SUPPORT ON FAILING MYOCARDIUM

The use of VADs to treat patients with refractory heart failure has permitted the study of human failing myocardium at two stages. Failing myocardial tissue can be obtained when the device is implanted, and at the time of removal for cardiac transplantation. The ability to obtain paired human myocardium at these two points has facilitated the detailed analysis of the effect of chronic mechanical unloading on the expression of various genes and proteins that typify the failing phenotype.[6]

While much is known about the responses of failing myocardium to pulsatile-type devices, there is little data available on the cellular and hemodynamic response of failing myocardium to continuous flow support. However, the Methodist DeBakey Heart Center has conducted a series of experimental studies that demonstrated that chronic mechanical support with the DeBakey VAD leads to decreases in cardiac myocyte size, collagen reduction and reduction of cardiac TNFα expression as well as normalization of dystrophin expression.[5,7] Thus continuous-axial flow support with the DeBakey VAD supports the circulation in a manner similar to that which has been observed with the pulsatile-flow devices.

The underlying hypothesis that unites much of the research into VAD-mediated cardiac recovery is that hemodynamic unloading of the failing heart allows reversal of the compensatory and stress responses of the overloaded myocardium, and results in structural and functional remodeling of the tissue, known as "reverse remodeling."[8]

CLINICAL BENEFITS OF MECHANICAL UNLOADING

The biological response of the failing heart to mechanical unloading includes the improvement of a large number of cellular markers that are abnormal in the failing phenotype. Furthermore, functional analysis, as shown by hemodynamics or electrical properties of the failing heart, may also improve. However, translation of these changes into improvements in function is a phenomenon that is difficult to study. Nevertheless, some patients regain cardiac function to the point that device removal is possible with some recovery of cardiac function. These improvements are ostensibly preceded by cellular, hemodynamic and electrophysiological alterations associated with reverse-remodeling.

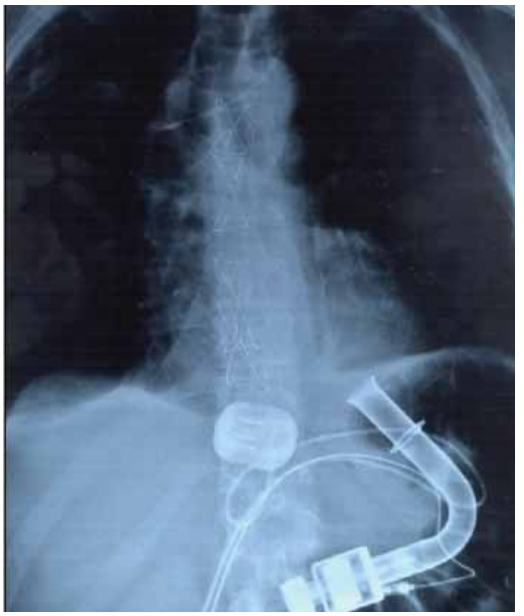

Figure 2.
Radiograph illustrating placement of the DeBakey-Noon pump. Left Ventricular Assist Devices (LVAD) are implanted in the left ventricle and deviate blood through the pump into the ascending aorta via an outflow graft.

CONCLUSIONS

Mechanical circulatory support via VADs has become a standard therapeutic option available to bridge patients with end-stage heart failure to cardiac transplantation, as well to provide some patients a definitive or destination therapy. Mechanical unloading of the myocardium may, in effect, re-set the progress of heart failure, and even potentiate device removal in some patients without the need for cardiac transplantation. Most of the work so far in this field has been developed with bigger, noisier pumps that are difficult to implant, and fully support the circulation via total left ventricular cardiac replacement.

Newer pumps provide continuous

Figure 3.
The Impella Recover System. The figure illustrates the relative size difference between the DeBakey VAD (left) and the Impella system (right), which can be percutaneously placed via the femoral artery.

axial-flow, and permit pulsatility depending on the degree of support utilized. Initial scientific observations and clinical experience with continual flow VADs reveal that improvement of myocardial function is possible in some patients, and perhaps future emphasis should be aimed at determining signals needed to enhance recovery, or the design of better devices that permit optimal physiological recovery.

The DeBakey VAD is at the front-stage of development in the use of continuous-axial flow support for chronic therapy, having been implanted in over 200 patients worldwide, and evaluated worldwide as a bridge to cardiac transplantation, as well as destination therapy. With regard to the effect of the DeBakey pump in failing myocardium, it appears continual support by this device induces beneficial cellular changes and therefore, may provide a strategy for myocardial recovery. In addition, a short-term continuous-axial flow pump that can be placed via the femoral artery, the Impella Recover System, is currently undergoing clinical trials. The first implant of this minimally invasive device was performed at the Methodist DeBakey Heart Center with functional success.

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MULTIPLE MYELOMA AND CARDIAC AMYLOIDOSIS

A 77-year-old white male, non-smoker with a two-year history of multiple myeloma (diagnosed by agarose electrophoresis with a finding of a monoclonal-free lambda light-chain in the gamma globulin region from a urine sample) presented with a six-month history of progressive dyspnea on exertion, fatigue, peripheral edema and enlarging abdominal girth. His oncologist reported clinical remission of the multiple myeloma but was referred to a nephrologist for evaluation of modest renal dysfunction (BUN 35, creatinine 2.5). Fluid retention and renal function subsequently improved with diuretic therapy. There was no prior history of cardiovascular disorder or hypertension. He had been a strenuous exerciser all of his adult life.

Physical examination revealed a right-pleural effusion, hepatomegaly, mildly positive HJ reflux and 2+ peripheral edema below the knees. No heart murmur or extra heart sound was heard. An electrocardiogram (Figure 1) indicated non-specific ST-T changes, low voltage and QS V1 through V3.

An echocardiogram (Figure 2) indicated concentric LVH, normal right- and left-ventricular chamber size and function, and mildly enlarged atria. PA pressure was estimated at 44 mmHg. Doppler findings were consistent with diastolic dysfunction manifested by impaired left-ventricular relaxation and marked increase in left-ventricular filling pressures (> 25 mmHg). Most striking was the speckled or granular appearance of the myocardium, consistent with a diagnosis of cardiac amyloidosis. No additional diagnostic studies were performed.

Six months after the onset of heart failure symptoms and four months after diagnosis by echocardiography, the patient remains alive. Present therapy consists of supportive measures.

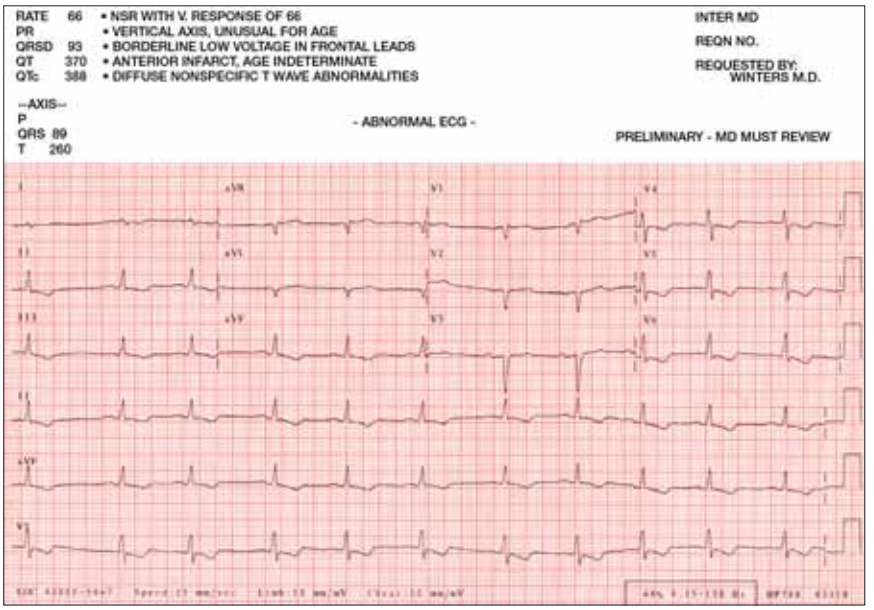
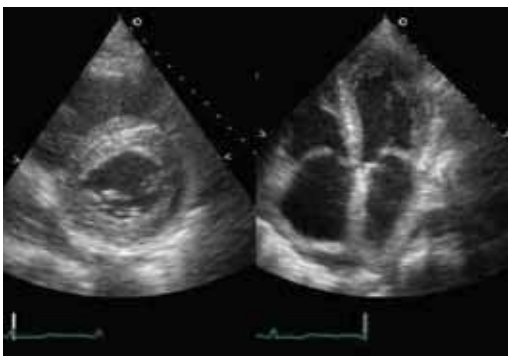
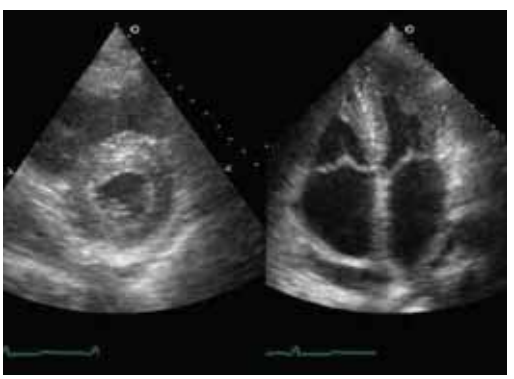


Figure 1.
ECG with low voltage; diffuse, no-specific ST-T changes. QS, V_1–V_3.



End diastole



End systole

Figure 2.
Echocardiogram. x section left: 4 chamber right. End-diastole. Speckled, granular appearance of the myocardium. Thickening of the ventricular walls, VS, atrial septum and valve leaflets.

Pathology: Deposition of protein myofibrils diffusely in the myocardium. The fibrils are immune globulin light chains often associated with multiple myeloma. Most cases involving the myocardium occur in primary amyloidosis. Cardiac involovement is often the main determinant of prognosis.

Demographics: M/F (60/40), median age 60 – 90 (M & F); age range 30-90 years; 97% over the age of 40. Caucasian 94%.

Tell-tale Signs: Macroglossia, periorbital ecchymoses, carpal tunnel syndrome.

Multisystem Features: Isolated heart involvement (uncommon). Renal: proteinuria, nephrotic syndrome. Neurology: autonomic neuropathy (anhydrosis, orthostatic hypotension, syncope). Gastrointestinal: hepatomegaly, diarrhea, weight loss. Hematology: multiple myeloma (uncommon).

Cardiovascular Symptoms: Fatigue, dyspnea, orthopnea, chest pain atypical for coronary ischemia. Coexisting CAD is uncommon. Sudden death (30%) not predictable by QTc interval or VT on Holter monitor.

Cardiovascular Findings: Findings of right heart failure predominant; most common findings (hepatomegaly, pleural effusion, peripheral edema, ascites, elevated JVP); S3, S4, systolic murmurs, pulmonary congestion, supine hypotension (14%); postural hypotension (40%).

Chest X-ray: Cardiomegaly, pleural effusions.

Electrocardiogram: Abnormal in 96%, low voltage (71%), pseudoinfarction pattern (75%). Intramyocardial vessel infiltration by amyloid may cause small vessel disease, R or LBBB (6%), 1st, 2nd, or 3rd AV block (25%).

Holter Monitor: Ventricular tachycardia (26%) documented in sudden or non-sudden death.

Echocardiography:

- Frequently diagnostic.
- Increased myocardial echogenicity with a granular, speckled, sparkling or ground-glass appearance (65%) (diagnostic), thickened ventricular septum (86%), ventricular walls, atrial septum, valve leaflets.
- Normal ventricular chamber size (97%).
- Normal systolic function (LVEF over 85% in 55%).
- Increased LV mass. Dilated atria.
- RV enlargement: late sign, severe disease, decreased survival

Doppler Flow: Restrictive filling pattern and impaired relaxation consistent with diastolic dysfunction. Mild to moderate incompetence common for all valves.

Survival: Median duration survival (M/F) following diagnosis of primary amyloidosis: 1.08 (0.83-1.25) years (95% C.I.). Sudden death: 34%. Survival in absence of heart failure: 2.34/1.56-2.92 years. When heart failure appears (33%) survival: 0.75 (0.59-1.00) years.

Predictors of Survival: Multivariate analysis: LV wall thickness, derived LV mass, EF. Doppler: Shortened mitral E-wave deceleration, increased E/A ratio.

For additional information or pathology and therapy, refer to these resources.

RESOURCES

1. *Otto CM. The practice of clinical echocardiography. 2nd edition. W.B. Saunders Co., Philadelphia, PA 2002; chapter 28:625-628.*
2. *Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, Falk RH. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. Q.J. Med 1998; 91:141-157.*
3. *Palladini G, Campana C, et al. Serum n-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. Circulation 2003; 107(19):2440-2445.*
4. *Kayaina J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. Circulation 2003; 107(19):2446-2452.*

ABOUT THE METHODIST DEBAKEY HEART CENTER

The Methodist DeBakey Heart Center continues the groundbreaking work begun by famed heart care pioneer, Dr. Michael E. DeBakey and his associates, who developed many of today's life-saving techniques, tools and procedures at The Methodist Hospital. Located in Houston, Texas, the Methodist DeBakey Heart Center combines research, prevention, diagnostic care, surgery, and rehabilitation services in a coordinated multidisciplinary program with one focus: delivering compassionate, effective care and treatment to patients suffering from heart disease.

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