Page 2 — Advanced Heart Disease Specialists Leading Expanded U.S. Clinical Trial of HeartMate 3 Left Ventricular Assist System
As one of the limited centers in the United States participating in the limited clinical trial program of the HeartMate 3™ centrifugal-flow chronic left ventricular assist system, the Brigham and Women's Hospital Heart & Vascular Center was among the first to implant this potentially game-changing technology in mechanical circulatory support.

Page 4 — Cardiovascular Genetics Center Specialists Identify How Mutations of the Titin Gene Cause Dilated Cardiomyopathy
Researchers in the Cardiovascular Genetics Center were the first to sequence the behemoth titin gene responsible for encoding the largest protein in the human body. They discovered that mutations truncating titin are the most common genetic cause of severe and familial dilated cardiomyopathy. Earlier this year, they expanded these studies to 5,000 individuals with a spectrum of cardiovascular physiology.

Page 6 — With Implanted Hemodynamic Monitor, Heart Failure Specialists Are Able to Reduce Hospitalizations and Improve Patient Care at Home
Heart & Vascular Center interventional cardiologists were among the first to implant the CardioMEMS™ Heart Failure System, after its recent FDA approval as an implantable hemodynamic monitor for heart failure patients. This first-of-its-kind implantable wireless device placed in a blood vessel in the lung provides remote monitoring of pulmonary artery pressure to reduce hospitalizations in patients with heart failure.

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Advanced Heart Disease Specialists Leading Expanded U.S. Clinical Trial of HeartMate 3
Left Ventricular Assist System

As one of the limited centers in the United States participating in the limited clinical trial program of the HeartMate 3™ centrifugal-flow chronic left ventricular assist system, the Brigham and Women’s Hospital (BWH) Heart & Vascular Center was among the first to implant this potentially game-changing technology in mechanical circulatory support.

This year, the U.S. Food and Drug Administration gave the go-ahead to broaden enrollment of the U.S. clinical trial to include more than 1,000 patients at up to 60 clinical sites. Mandeep R. Mehra, MD, Executive Director of the Center for Advanced Heart Disease and Medical Director of the Heart & Vascular Center, is one of four national co-principal investigators leading the trial and chair of the publications and presentations committee.

**Next-Generation Technology**

The HeartMate 3 LVAS is a third-generation mechanical circulatory support device, engineered with the promise for enhanced hemocompatibility. It features a centrifugal-flow durable left ventricular assist system that utilizes fully magnetically levitated technology designed to lower adverse event rates, especially hemocompatibility complications (i.e. thrombosis). Evidence of enhanced hemocompatibility was demonstrated in the first 50 patients receiving the HeartMate 3 at 10 centers in Europe, Australia and Canada, where no device thromboses occurred and no pump exchanges were required in the first six months post implantation.

“The HeartMate 3 technology includes several design features aimed at enhancing durability and hemocompatibility,” said Dr. Mehra. “A miniaturized centrifugal flow device gives it a smaller profile and fewer moving parts than previous generation left ventricular assist devices, which also helps with ease of surgical placement.” He explained that, “Magnetic levitation technology spins the rotor and keeps it in a stable position at a broad range of speeds, while the internal pulsatility with automatic changes in speed produces an intrinsic pulse to minimize pump stasis.”

In addition, large gaps between the rotor and the pump housing allow for improved blood flow with minimized shear stress on blood components and internal sintering with textured titanium microspheres creates a more biocompatible surface.

“HeartMate 3 can be used either as a short term device to bridge patients to transplantation or as a long-term lifetime therapy,” said Dr. Mehra.

**MOMENTUM 3: The Largest LVAD Trial to Date**

With Dr. Mehra participating as national co-principal investigator of the MOMENTUM 3 (Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy with HeartMate 3) clinical trial, the Center for Advanced Heart Disease is at the forefront of evaluating this technology in the largest LVAD clinical trial to date. More than 1,000 patients with advanced heart failure will be randomized to either the HeartMate 3 or its predecessor, the HeartMate II device, to evaluate survival free from device replacement and debilitating stroke in both the short term (six months) and long term (two years).

This pivotal non-inferiority trial will start with 294 patients followed for six months to evaluate the short-term indication of bridge-to-transplantation therapy, after which an additional 72 patients will be added (total of 366) and followed for two years to evaluate long-term use as a destination therapy. Beyond the pivotal trial cohort, approximately 600 additional patients will be enrolled to assess the superiority of HeartMate 3 to HeartMate II on pre-specified secondary endpoints.

“The all-comers population of advanced stage heart failure patients in this trial is somewhat unique for an LVAD trial, where typically devices are studied either for use as bridge-to-transplantation or for destination therapy,” explained Dr. Mehra. “But patients do not always fit neatly into these two categories, nor do they always remain in their initially assigned category. Research shows that about one-third of patients initially slated to undergo heart transplantation remain on LVAD support for more than two years, and nearly half of these patients may be eventually removed from the transplant list.”

In addition, among patients who undergo LVAD implantation, those who are ineligible for transplantation tend to have modestly poorer outcomes compared with transplant candidates, who are typically younger and have fewer co-morbidities.
At the Forefront of LVAD Research
The Center for Advanced Heart Disease at BWH is an internationally-recognized center of excellence in the diagnosis and treatment of heart failure and its complications. Areas of strength include the management of chronic heart failure across the spectrum of disease severity, judicious utilization of mechanical circulatory support and cardiac transplantation, cardiovascular genetics (including inherited cardiomyopathies such as hypertrophic cardiomyopathy), cardio-oncology, and pulmonary hypertension/right heart failure.

As well, the Center has taken a leadership role in the national registry for mechanical circulatory support (INTERMACS) representing over 15,000 patients in the United States, the parallel registry for medical outcomes (MEDAMACS) in patients progressing toward mechanical circulatory support.

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Surgical Director, Right Heart Rescue and Pulmonary Thromboendarterectomy,
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The Heart & Vascular Center at Brigham and Women’s Hospital continues to lead New England in pioneering advanced therapeutics. Recent milestones include:

2015 First implant of the New Generation HeartMate 3 LVAD
2013 First elective explant of a long-term left ventricular assist device for myocardial recovery
2012 First total artificial heart implant

Advanced Heart Failure/Cardiomyopathy Program – Contact Us
The Advanced Heart Failure/Cardiomyopathy Program at BWH offers comprehensive inpatient and outpatient clinical services to adults with cardiomyopathy and heart failure, from diagnosis to cardiac catheterization to innovative medical- and device-based treatments.

Contact our experts at (857) 307-4000 to learn more about management and treatment options for patients with advanced heart disease.

Heart & Vascular Center Access Information
For more information on the Heart & Vascular Center and our programs and services, please contact us at BWHHeartandVascularCenter@partners.org.

To reach us immediately for patient-related issues:

- For an ambulatory consultation or to reach a specific physician or researcher: (857) 307-4000
- For direct inpatient transfers and cardiovascular interventional procedures: (617) 543-4170
- For direct assistance with patient referrals and consultations with one of our specialists, please contact physician liaison Ellen Steward at (617) 582-4733 or esteward@partners.org
Cardiovascular Genetics Center Specialists Identify How Mutations of the Titin Gene Cause Dilated Cardiomyopathy

Three years ago, Christine Seidman, MD, Director of the Cardiovascular Genetics Center, and colleagues were the first to sequence the behemoth titin gene responsible for encoding the largest protein in the human body. They discovered that mutations truncating titin are the most common genetic cause of severe and familial dilated cardiomyopathy (DCM) (N Engl J Med 2012;366:619-28).

Earlier this year, they expanded these studies to 5,000 individuals with a spectrum of cardiovascular physiology. They showed that titin mutations are the most common genetic cause for DCM in ambulatory patients and identified clinically important manifestations and outcomes for patients with titin mutations (Sci Trans Med. 2015; 14:270). They discovered how titin mutations do their damage to the heart muscle. Truncating titin mutations prevent development of the normal cardiomyocyte structure and impair the cardiomyocyte’s contractile performance (Science 2015; 349:982 -86).

Sequencing Titin

Using next-generation sequencing, Dr. Seidman and colleagues sequenced the enormous titin gene in more than 5,000 individuals, including over 600 patients with dilated cardiomyopathy, over 3,000 community-based participants in the Framingham and Jackson Heart Studies with longitudinal cardiovascular data, and over 300 healthy controls. The researchers correlated the presence of mutations that truncated titin with the clinical manifestations in each cohort.

“We found that truncating titin mutations were present in 20 percent of patients with severe and in 13 percent with mild dilated cardiomyopathy,” said Dr. Seidman. These mutations were associated with marked reductions in the contractile function of the heart and increased the risk for arrhythmias. “We were also able to reveal that the location of the mutation mattered. Only truncating mutations that are predominantly in the titin A-band region were strongly associated with dilated cardiomyopathy,” added Dr. Seidman, “whereas other mutations, particularly those in the I-band, did not cause disease.”

To understand the different consequences in titin mutations, the laboratory characterized titin expression in human heart tissues. These studies showed that titin molecules in human hearts universally incorporated A-band sequences, but only variably incorporated I-band sequences. A mutation that altered sequences that are rarely expressed in the human heart would have little or any adverse consequences on contractile function.

“These findings have improved the accuracy of clinical genetic tests, which allows these to accurately screen relatives at risk for dilated cardiomyopathy. In addition, establishing genotype-phenotype correlation in the management of patients’ dilated cardiomyopathy due to titin mutations can be improved by early surveillance and interventions,” explained Dr. Seidman.”

Investigating the Damage

To determine how truncated titin does its damage, Dr. Seidman and colleagues produced a cellular model of dilated cardiomyopathy – cell cultures of human cardiomyocytes with titin mutations that are derived from induced pluripotent stem cells. With collaborators in Dr. Christopher Chen’s laboratory at Boston University these cardiomyocytes were used to develop micro-cardiac tissues that contract, produce force, and respond to stimuli.

Since titin is known to be responsible for sensing and responding to myocardial stresses, Dr. Seidman and her colleagues suspected that titin truncating variants might exhibit aberrant stress responses. “We found that micro-tissues made from car-
diomyocytes with titin mutations were less able to respond to mechanical and beta-adrenergic stress and had impaired growth factor and cell signaling activation,” she said. “These deficits are expected to impair cardiac adaptation to increased mechanical load and stress signals.”

The team also studied titin protein in cultures of human cardiomyocytes with titin truncating mutations. Some produced a stable truncated protein, a surprising observation. However, these mutant proteins did not assemble with other contractile proteins into well-organized functional sarcomeres. “The sarcomere is the contractile unit of muscle cells. Poorly organized sarcomere could account for basal contractile deficits and attenuated signaling,” explained Dr. Seidman.

RNA-sequence analyses also indicated that titin truncating mutations affected cardiomyocyte signaling and RNA expression. Notably there was diminished expression of several growth factors. “Interestingly, the growth factor deficit could be partially overcome by supplementing the cardiomyocytes with the vascular endothelial growth factor (VEGF),” she said.

Looking Ahead

“Based on this research,” Dr. Seidman said, “we can explain why patients with specific titin truncating mutations develop dilated cardiomyopathy and we now have some clues about potential therapeutic approaches to help limit the disease and its progression to heart failure.”

With titin mutation as a target of therapy, pharmacologic agents could be developed to enhance titin gene expression, increase sarcomere formation, or stimulate cardiomyocyte signals that improve function.

Christine Seidman, MD
Director, Cardiovascular Genetics Center,
Brigham and Women’s Hospital

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Levine Cardiac Intensive Care Unit Celebrates 50th Anniversary

When the Levine Cardiac Unit opened in February 1965, at the Peter Bent Brigham Hospital, one of the predecessor institutions to today’s Brigham and Women’s Hospital (BWH), it was one of a handful of novel, specialized coronary care centers that would revolutionize both the care and survival of heart attack patients.

The Levine Unit was specifically designed and staffed to monitor heart rhythm and resuscitate patients experiencing fatal arrhythmias. It was, at the time, a remarkable facility, equipped with electrocardiographic monitors for continuous heart rhythm surveillance, alarms to alert staff of rhythm derangements, and highly trained coronary care nurses schooled in electrocardiographic pattern recognition and well-prepared to intervene during cardiac arrest.

As the Levine Cardiac Intensive Care Unit (CICU), the name it has evolved into, celebrates its 50th anniversary, hospitals throughout the world have cardiac intensive care units where patients who reach the hospital in time after a heart attack will very likely survive; a dramatic change from 50 years ago when as many as a third of heart attack patients would die before leaving the hospital.

“The longest-running director of the Levine CICU, Elliott Antman, MD, (1980-2009), helped to shape the modern era of coronary care and its improved outcomes; such that the majority of heart attack patients in the Heart & Vascular Center are now able to be treated in cardiac step-down units,” said David A. Morrow, MD, current Director of the Levine CICU. “Today the Levine CICU is located in the Shapiro Cardiovascular Center at BWH, where it continues to lead the way in caring for the most complex critical cardiac patients and training the next generation of world leaders in the field through an innovative fellowship pathway in critical care cardiology.”

Invented Defibrillation and Cardioversion

In 1962, Bernard Lown, MD, became the first clinician to apply direct current (DC) electrical shock to halt life-threatening ventricular tachycardia. Others’ attempts at alternating current electrical cardioversion had been partly successful, but alternating current induced fibrillations in about one quarter of cases. With his invention of the DC defibrillator and cardioverter, a safe and reliable method of delivering a life-saving shock to the heart was realized. In 1965, Dr. Lown became the first director of the Levine Cardiac Unit.
Interventional cardiologists at the Brigham and Women’s Hospital (BWH) Heart & Vascular Center were the first in New England to implant the CardioMEMS™ Heart Failure System, after its recent FDA approval as an implantable hemodynamic monitor for heart failure patients. This first-of-its-kind implantable wireless device placed in a blood vessel in the lung provides remote monitoring of pulmonary artery pressure to reduce hospitalizations in patients with heart failure.

Deepak L. Bhatt, MD, MPH, Executive Director of Interventional Cardiovascular Programs, who implanted and calibrated the device in the catheterization laboratory, explained, “Patients can send their internal heart pressures from home every day to a central monitoring site that detects changes and provides alerts to their care team.”

“By detecting rising pulmonary pressure early, physicians are able to adjust therapy in time to avert decompensation and avoid hospitalizations,” said Lynne Stevenson, MD, Director of the Cardiomyopathy and Heart Failure Program.

Reducing Heart Failure Hospitalizations

In the CHAMPION trial of CardioMEMS, Dr. Stevenson, Michael M. Givertz, MD, and colleagues evaluated hemodynamically guided heart failure management using the CardioMEMS device to monitor pulmonary artery pressures in patients with New York Heart Association (NYHA) Class III heart failure. In patients with preserved ejection fraction, there was a 33 percent reduction in hospitalization during the blinded randomized period when only the physicians knew the results of monitoring, increasing to 48 percent reduction with use in the real-world setting in patients in whom they were being monitored. (Lancet 2015; released on line November 8, 2015).

Furthermore, the reduction of hospitalization was almost 50 percent in patients with heart failure with preserved ejection fraction (Circ Heart Fail. 2014; 7:935-944). “This is a remarkable advance for care of a population for whom no other therapies have been shown to have any benefit,” said Dr. Stevenson. “In this population alone, we could anticipate a reduction of up to 250,000 heart failure hospitalizations annually. An additional unique impact of this strategy is reduction not only of heart failure hospitalizations, but all-cause hospitalizations and particularly due to hospitalizations for pulmonary disease, which can be exacerbated by heart failure.”

Heart failure specialists in the trial were able to make more precise adjustments in diuretic and vasodilator therapies when they had information on pulmonary artery filling pressures from the device than when they did not have that information.

“The device is designed to alert clinicians when a therapeutic change is needed to halt rising filling pressures sooner than would be the case if we waited for patients to report weight gain or increased symptoms,” explained Dr. Stevenson. “Monitoring filling pressures on a daily basis has allowed us to intervene much earlier to more effectively manage heart failure, keeping patients feeling better and out of the hospital.”

Improving Patient Care

Akshay Desai, MD, MPH, Director of the Heart Failure Disease Management Program, explained how BWH heart failure specialists are leveraging the CardioMEMS technology to improve patient care. “CardioMEMS fits very well into our integrated heart failure management program, where nurses specializing in heart failure management have close, ongoing contact with our heart failure patients at home,” said Dr. Desai, who is an active investigator on a forthcoming manuscript that validates the algorithm for changing medications according to the pulmonary pressures. “CardioMEMS has enhanced that relationship to improve the care of our heart failure patients.”

When increased filling pressures are detected, a heart failure nurse calls the patient to discuss his or her medications, diet, and fluid intake to ascertain which factors likely contributed to the increased filling pressures. Changes can then be made to medications, diet and fluid intake so that filling pressures are reduced and decompensation is averted without the patient having to suffer from worsening symptoms.

Hemodynamic monitoring with CardioMEMS has also led to a surprising benefit that could not be appreciated when
Pulmonary Vascular Disease Specialists Add Balloon Angioplasty as a Treatment Option for Patients Not Eligible for Surgery

Percutaneous balloon angioplasty joins surgical thromboendarterectomy and acute embolectomy in the arsenal of therapies offered at the Brigham and Women’s Hospital Heart & Vascular Center that aim at revascularizing pulmonary vessels to improve ventilation, flow balance, and right-ventricular function.

“Balloon angioplasty may be a valuable option for clearing vascular obstruction in patients who are not candidates for surgical thromboendarterectomy and those who have had a less-than-optimal outcome from surgical intervention,” said Aaron Waxman, MD, PhD, Director of the Pulmonary Vascular Disease Program.

“While the surgical approach can effectively clear obstructions in the larger proximal pulmonary vessels, balloon angioplasty is capable of reaching and restoring blood flow in the narrower, more distal vessels,” he explained. “The goal is to intervene in vessels that are situated to maximize downstream improvement of blood flow.”

“Often, there are several vessels to treat,” said Dr. Waxman. “A less-invasive option, like balloon angioplasty, allows us to take a staged approach, treating five to eight vessels at a time during several procedures. And because cardiopulmonary bypass is not required during balloon angioplasty, there is no ischemia-reperfusion injury so patients often feel better sooner after the procedure.”

Balloon angioplasty for pulmonary lesions is considered by some experts to be a less-complete solution than thromboendarterectomy and, in some ways, it is. After surgical intervention, many patients will no longer need medical therapy, which is not often the case after angioplasty.

“Balloon angioplasty is not intended to replace thromboendarterectomy,” explained Michael J. Landzberg, MD, Director, Boston Adult Congenital Heart (BACH) and Pulmonary Hypertension Group. “It rounds out the full arsenal of pulmonary vascular disease therapies, making the Heart & Vascular Center prepared to treat all aspects of pulmonary artery disease, whether a patient needs revascularization of proximal or distal vessels or an emergency embolectomy.”

“Balloon angioplasty may also have potential as a bridge therapy to prepare complex patients for surgical intervention or as part of a hybrid surgery-angioplasty approach in patients with complex disease,” said Dr. Mehra.

Emergency Pulmonary Embolectomy
This large saddle pulmonary embolism was removed during emergency pulmonary embolectomy in a 64-year-old woman who presented with shortness of breath a few weeks after a bilateral hip replacement. Rapid assessment revealed the large saddle embolism and evidence of right ventricular dysfunction. Hari Mallidi, MD, Surgical Director of Right Heart Rescue and Pulmonary Thromboendarterectomy in the Pulmonary Heart Disease Program within the Heart & Vascular Center, performed an emergency embolectomy to remove the clot resulting in improved right heart function. The patient was discharged within one week to complete her hip replacement rehabilitation therapy at home.

Pulmonary Vascular Disease Program – Contact Us
The Pulmonary Vascular Disease Program at BWH provides highly-specialized, multidisciplinary evaluation and care for patients with complex pulmonary vascular conditions, including unexplained dyspnea, pulmonary arterial hypertension, and pulmonary hypertension associated with heart disease, COPD, chronic thromboembolic disease, liver disease, and other conditions.

Contact our experts at (857) 307-4000 for more information or to refer a patient to our Pulmonary Vascular Disease Program.

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With Implanted Hemodynamic Monitor, Heart Failure Specialists Are Able to Reduce Hospitalizations and Improve Patient Care at Home... continued from page 6

patients in the trial were unaware of their monitoring. “When we tell our patients that their pressures are rising, they often remember what they did wrong in the last 48 hours. For example, they often describe eating very salty foods or forgetting to take their medications,” explained Irene Cooper, RN, an experienced coronary care unit nurse now monitoring the CardioMEMS patients.

“When patients receive direct feedback in real time about their heart pressures, they are empowered to change their behavior, resulting in better pressures and better heart function,” explained Eldrin F. Lewis, MD, MPH, Director of the Cardiovascular Clerkship Program. “Some patients make important changes like reducing their salt and fluid intake, and then make the connection over time to feeling better with more normal pressures and less shortness of breath.”

“Obviously, we hoped that the data from the device would help us as physicians manage heart failure more effectively and keep patients out of the hospital,” said Dr. Stevenson. “What we did not anticipate was that patients would, in turn, give us important clues about what had caused their pressures to rise, and how to improve their own health.”

Dr. Stevenson and her colleagues are now leading a Master’s Program on hemodynamically-guided heart failure management, where BWH physicians and expert monitoring nurses share their experience with CardioMEMS to help clinicians from around the world utilize this new strategy to help their patients feel better and stay out of the hospital.

Interventional Cardiology – Learn More from Our Specialists
Contact our experts at (857) 307-4000 to learn more about the latest interventional cardiology treatments for heart failure patients.