

Peter Munk Cardiac Centre

CLINICAL AND RESEARCH REPORT



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HEART FAILURE MANAGEMENT

100 and counting

CELEBRATING A CARDIOVASCULAR MILESTONE

On February 16th of this year, surgeons at the Peter Munk Cardiac Centre reached an impressive milestone with the implantation of its 100th left ventricular assist device – or LVAD as it is more commonly known.

Often referred to as a “bridge to transplant”, a ventricular assist device is a type of sophisticated miniature mechanical pump that can be implanted on one (more commonly the left) or both sides of the heart. It regulates blood pressure, circulation and organ function.



From left, Dr. Viv Rao, Andrea Clegg, Dr. Heather Ross, and David Prince gave moving testimonies about the LVAD program from the doctor and patient perspectives.

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ABOUT THE PETER MUNK CARDIAC CENTRE

The Peter Munk Cardiac Centre is the premier cardiac centre in Canada. Each year, approximately 37,000 patients receive innovative and compassionate care from the Centre’s world-renowned multidisciplinary heart team. The Peter Munk Cardiac Centre is based at Toronto General Hospital and Toronto Western Hospital. Both hospitals, along with Princess Margaret Hospital, are part of University Health Network. All three are research hospitals affiliated with the University of Toronto.



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Its primary role is to act as a temporary assist to keep a diseased or damaged heart functioning until a replacement heart is located – hence the term “bridge to transplant”.

In some cases, the LVAD is in place for only a few days, while in others it may help to keep the heart functioning for years. In fact, one patient recently marked his 567th day on an LVAD implanted at the Centre. In some cases, patients have even recovered to almost full heart function whilst using an LVAD, essentially eliminating the need for a transplant – but these cases are rare.

More often than not, the LVAD is a temporary bridge, and the patient will eventually receive a transplanted heart. That is where the invaluable support of heart donors comes in.

“If it wasn’t for our donors, we would never have been able to implant either the first or the 100th LVAD,” noted Dr. Heather Ross, Medical Director, Cardiac Transplant Program and the Ted Rogers and Family Chair in Heart Function, at the recent celebration of the 100th LVAD procedure held at the Centre. This sentiment was echoed by patients Andrea Clegg and David Prince, who spoke eloquently about how the LVAD program had positively impacted and saved their lives. Their presence alone provided strong testimony for Dr. Ross’ statement; “Our patients are the reason we do what we do.”

While the celebration was a fitting way to mark what Dr. Viv Rao, Surgical Director of the Cardiac Transplant Program and the Alfredo & Teresa DeGasperis Chair in the Surgical Management of Heart Failure, called, “a great milestone”, he was quick to point out that the program could not afford to rest on its laurels.

While Dr. Rao and Dr. Ross, along with an impressive team of cardiologists, cardiac surgeons, fellows, nurses, researchers and other staffers have helped to revolutionize the treatment of heart failure, there is still much work to be done.

Advanced heart failure is fast becoming an epidemic in Canada, and almost half of all individuals with this condition die within two years. Over 2,000 patients in Canada need a heart transplant. There are simply not enough hearts available through donors, so other therapies and options are needed.

Demand for LVAD devices continues to grow at the Peter Munk Cardiac Centre. The Centre is well on the way to the busiest year ever, having implanted their ninth LVAD by the end of May.

As such, the Peter Munk Cardiac Centre needs to continue improving the management of heart failure. And that means continually improving and perfecting the use of LVADs.

In addition to marking the 100th procedure, 2011 has also seen the introduction and evaluation of the ‘next generation’ LVAD technology, including the state-of-the-art Duraheart™ and Heartware™ devices. The Centre has also now amassed the largest Canadian experience with magnetically-levitated heart pumps, and is actively involved in clinical and basic science research on ventricular assist devices.

A proud history

1985 saw the first heart transplant in Ontario, performed at the Peter Munk Cardiac Centre.

Since then over 567 heart transplants have been done.

A total of nine advanced left ventricular assist devices (LVADs) are now available to the cardiologists and surgeons at the Centre, the largest number in Canada.

Last year alone, 20 LVADs were implanted at the Centre.

The Ontario Ministry of Health has recently agreed to limited funding for LVADs when used as a bridge to transplant. This important decision paves the way for more sustainable funding for the Centre program. However, at present, this funding covers just over half of the program costs.

Funding is needed to allow the Centre to tackle the still-existing limitations of the currently available range of LVADs, such as battery power, limited lifespan and other factors.

“The technology has improved,” points out Dr. Rao. “The devices are smaller and last longer, and there are better outcomes, with over 70 per cent survival after two years. But we still need to make these devices more easily implantable, more cost efficient, and, of course, more effective for the patient.”

“But that is part of our mandate here at the Centre,” he concludes. “To explore new technologies, and go where no one has gone before.”



RESEARCH

From the lab to the clinic

RESEARCH BREAKTHROUGH HOLDS PROMISE FOR NEW THERAPY

At first glance, the science seems baffling for the lay person. But the recent publication of research led by Drs. Sonya Hui and Jaehyun Choi, under the supervision of Dr. Mansoor Husain, Director of Research for the Peter Munk Cardiac Centre, may lay the path for an improved approach to angioplasty, a technique used to treat atherosclerosis, blockage of the arteries, and similar cardiovascular conditions.

Recently published in *Circulation Research*, the paper's title is a mouthful: 'A calmodulin-binding site on cyclin E mediates Ca²⁺-sensitive G1 transitions in vascular smooth muscle cells.' But as Dr. Husain points out, the content essentially discusses the design of a new peptide – a molecule consisting of two or more amino acids, which is essentially a fragment of a protein – at the Centre.

This peptide has been modified and tagged to interrupt the binding of two specific proteins: calmodulin and cyclin E. Previous work by Dr. Choi, also published in *Circulation Research* five years ago, described how these two proteins bind. The new work takes that further and looks at what happens if that binding is blocked or interrupted.

All of this has implications in the vascular smooth muscle cells (VSMC) found in the walls of blood vessels carrying blood to and from the heart. One of the key objectives of the researchers, who were primarily funded by the Canadian Institutes for Health Research, was to identify which cell cycle proteins in VSMC were responsive to changes in cell calcium. They found that blocking the binding of these proteins, one of which mediates the calcium responsiveness, stops the

proliferation, or excess growth, of VSMC, which can lead to the formation of scar tissue inside the artery.

While the pure science behind this work is impressive enough and will influence future studies around the world, Dr. Husain has more direct expectations. "As a cardiologist, I see a very practical potential application for this research," he states. Dr. Husain and his team are hopeful that this research may lead to an improved approach to angioplasty, a technique used to widen narrow or obstructed blood vessels in heart conditions such as atherosclerosis. In a significant percentage of cases, this condition is treated by use of a coronary artery stent, a metal tube or framework that is inserted into the artery to help keep it open. However, since the stent is a foreign object, the body's immune system responds to it. In addition to healthy cells covering over the stent, scar tissue can also build up inside the stent and begin to block the artery anew. In addition, blood clots can occur within the stent.

"Thousands of angioplasties are conducted throughout Canada each year," says Dr. Husain. "When we don't use stents that elute drugs designed to block VSMC proliferation, about 30 percent of patients have their blood flow restricted again by this renarrowing of the arteries, or restenosis." The use of drug-eluting stents that release powerful drugs that suppress local inflammatory responses and VSMC growth can lessen the problem, but these drugs can also negatively impact the beneficial cells covering over the stent. The result can be unwanted side effects, often necessitating the use of additional



Dr. Mansoor Husain believes the research led by Dr. Sonya Hui and Dr. Jaehyun Choi could eventually lead to better patient outcomes.

medications, such as blood thinning agents, to compensate.

Dr. Husain's hope is that the work on the new peptide will lead to a "kinder, gentler solution" to this problem. "Think of the cells that grow over the stent in terms of a lawn," he explains. "With a lawn, you want to eliminate only the weeds and not interfere with the lawn. In a similar way, we need a therapy that will act on the harmful cells that cause scarring, but not touch the beneficial endothelial cells that we want to form over the stent."

The path from this research to a therapy that will achieve this goal is still a long one; Dr. Husain is quick to point out. "We have obtained a patent and licence for development with a small Canadian company, and hope to move forward steadily," he notes. "We have proof of principle, but more development and targeted funding is needed to move from the lab to in vivo testing, and hopefully eventually to clinical trials."



A C H D

Caring for the 'first generation'

MEETING THE CHALLENGES OF ADULT SURVIVORS OF CHD



Dr. Louise Harris has seen many breakthroughs in the treatment of adult congenital heart disease emerge from Toronto over the past 20 years.

In many ways, it can be called the price of success. But this price – meeting the complex medical challenges of caring for the first true generation of adult survivors of congenital heart disease – is one that the Peter Munk Cardiac Centre is more than thankful to pay.

"We are now seeing the first generations of Canadians born with congenital heart disease who have reaped the benefits of the advances in surgery and other therapies in childhood and have survived into adulthood," explains Dr. Louise Harris, Professor of Medicine at the University of Toronto and staff cardiologist at the Peter Munk Cardiac Centre.

As Dr. Harris points out, the Adult Congenital Heart Program at the Centre has played a major role in improving the outlook of patients with congenital heart disease. "The Centre has been a real pioneer in this area," she says. "The group has published widely in the clinical literature over the past 20 years and influenced the management of ACHD internationally. Work from the group contributed substantially to the *Canadian Consensus on the Management of Adults with Congenital Heart Disease* released in 2009, and was also referenced in the original U.S.

guidelines on this subject.

As a result of improved management of congenital heart disease, patients are living longer than ever before. "In fact, there is a commonly-quoted statistic that there are now more adults with congenital heart disease in Canada than children with this condition," Dr. Harris points out.

But as these patients enter adulthood, they often do so with already compromised cardiovascular systems. "The result is a whole new range of medical issues that we need to understand and learn how to manage," she notes. Among these issues, and the one Dr. Harris is most closely involved with, is how to manage heart rhythm disorders in ACHD patients.

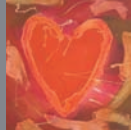
"Several years ago, Dr. Gary Webb, the founder of the Program, would send ACHD patients with heart rhythm problems to the electrophysiology group, but we were uncertain how to deal with the unique challenges they presented," she says. "So we started to look, but found there was little useful literature or clinical experience. Most of the knowledge base had been built from experiences with children with congenital heart disease or extrapolated

from non-ACHD adult patients with arrhythmias. We were really looking at a blank page."

Through a series of research initiatives over the past 20 years, Dr. Harris and her colleagues at the Centre have played a major role in filling in that page. For example, working under the leadership of Dr. Eugene Downar, an electrophysiologist, and Dr. Bill Williams, a cardiac surgeon from Sick Kids Hospital, an interoperative mapping system was designed that allowed better understanding of the mechanisms of certain heart rhythm problems.

"We have a much better understanding of which ACHD patients are at risk of developing rhythm disorders, and who might be at a risk of sudden death," says Dr. Harris. "We know these patients need to be managed differently. For example, even the use of pacemakers or, more recently, defibrillators, which are commonly used to correct rhythm disorders in others, present specific challenges in individuals with ACHD. In the same way, corrective surgery approaches need to be different due to the compromised anatomy of the heart and vascular system."

As the numbers of these patients continue to grow, they will have a huge impact, both from the clinical and economic perspective. This population will require medical interventions earlier and potentially for a longer period of time. The team at the Centre under its current leader, Dr. Erwin Oechslin, is focusing its research efforts on this important emerging population and, more importantly, on how to translate the research into ways to provide the best, most effective, clinical care.



PSYCHOLOGY

Preparing for the final journey

LEARNING TO COPE WITH END-OF-LIFE ISSUES



Helping patients and their care teams face the ultimate reality of death is the focus of Dr. Adrienne Kovacs' research.

"It's one of the hardest things our cardiologists have to do," comments Dr. Adrienne Kovacs, a psychologist in the Adult Congenital Heart Program at the Peter Munk Cardiac Centre.

What Dr. Kovacs is referring to is not some new surgical technique or groundbreaking therapy – it's dealing with the ultimate death of a patient. In spite of the tremendous advances in the treatment of adult congenital heart disease (ACHD), and the world-renowned clinical record and academic leadership of the Toronto group, it is a hard fact that some patients will eventually, unavoidably, succumb to the complications of ACHD. It can be a traumatic experience that impacts everyone involved, from patients facing the end of their lives, through family members, to the doctors and other members of the care team – many of whom may have known and treated the patient for years.

As such, providing the best possible

end-of-life care is vital, yet this is an area relatively unexplored in cardiac care, especially when it comes to ACHD. Dr. Kovacs and her colleagues at the Centre are working hard to change that.

"There is a good base of knowledge and clinical experience in oncology and even other heart conditions that affect older patients," notes Dr. Kovacs. "But in ACHD, our knowledge and resources are lacking."

A Toronto native, Dr. Kovacs is the only full-time psychologist working with ACHD in North America. She combines clinical work with ground-breaking research, and a major area she has focused on recently is end-of-life issues in patients with complex ACHD.

"ACHD is different than other heart disorders," she explains. "Patients enter the medical system at birth, not in their 50s or 60s as is common with

other conditions. They transition from pediatric care to adult care. But they frequently do so with complex congenital conditions and chronic disease. And even though the advances in treating congenital heart disease represent one of the greatest success stories in modern medicine, many patients remain at risk of premature death."

Dr. Kovacs is the only full-time psychologist working with ACHD in North America. She combines clinical work with ground-breaking research, and a major area she has focused on recently is end-of-life issues in patients with complex ACHD.

Spurred in part by the initiative of Drs. Daniel Tobler and Matthias Greutmann, at the time clinical fellows in ACHD at the Centre and now practicing in that field in their home country of Switzerland, Dr. Kovacs is now devoting herself to research into end-of-life issues facing ACHD



patients. She is the senior author of a recent paper on the subject in the *International Journal of Cardiology*, and also of another paper currently pending publication in *Palliative Medicine*.

“The focus of the research is to examine the specific experiences of ACHD patients facing the end of their lives”, Dr. Kovacs states. “In this way, we can better understand the issues that are important to them, compare the similarities and differences compared to patients with other conditions, and generally find out as much as we can.”

The ultimate goal is to learn from this research to develop effective strategies and tools that can be used to improve the end-of-life experience for patients. “But before we can develop newer, more effective strategies, we need to know exactly where we are,” Dr. Kovacs says. “We need to know what patients

want, and what types of initiatives they best respond to.”

“We already know that our ACHD care teams are eager to improve the way they handle these issues, and they want the tools and resources to help them do this,” she continues. “I’ve been so impressed by their overall commitment to their patients and their dedication to improving care through the entire spectrum of the diseases they deal with, including the end stages.”

As Dr. Kovacs stresses, research and clinical care “go hand-in-hand” at the Centre, and a major part of her work involves providing members of the ACHD care teams with updates on her research and information and expert advice on dealing with end-of-life issues through teaching rounds and other initiatives. She is also a key member in a year-old task force at

the Centre working to improve patient care in this area.

“There are important things we have learned that can be put to immediate and practical use,” she says. “For example, we know that almost 75% of patients in these circumstances want their doctors to discuss end-of-life issues. So we are teaching cardiologists and our other care providers to ‘invite’ these discussions.”

Although the percentage of ACHD patients who may need end-of-life care may now be small, Dr. Kovacs stresses that as the number of ACHD patients continues to grow, and as individuals in this group are living longer, our clinical practice needs to evolve and improve. And the research currently being done and shared will add to the Centre’s 50 year plus record of helping to improve the treatment of ACHD around the world.

ACHD: A life-long challenge

Congenital heart disease (CHD) is caused by a structural problem, or defect, in a baby’s heart that is present at birth. An estimated 1% of all live-born have a congenital heart defect. In Canada, this relates to approximately 4,600 babies born each year. Congenital heart disease can be caused by genetic or environmental factors, or a combination of both.

While many CHDs are minor and require no medical treatment, others can be very serious. In fact CHD is still the leading cause of death from birth defects during the first year of life. However, improvements in cardiac surgery and treatment of infants and children with CHD over the past few decades – many of them pioneered right here in Toronto - have dramatically reduced mortality rates.

Today, most patients reach adulthood, but carry with them the lingering effects of their heart defect and/or complications arising from surgical treatment – sometimes multiple surgeries – received in infancy or childhood. The result is a rapidly growing population of men and women with adult congenital heart disease (ACHD) who require ongoing medical care.

Currently, there are approximately 12,000 patients in the data base of the Adult Congenital Heart Program at the Peter Munk Cardiac Centre. The program is world renowned for its treatment and research expertise in ACHD. In fact, it is the largest and oldest centre of its kind in the world. The program celebrated its 50th anniversary in 2009, and is rated as providing “the gold standard” of care for adults with congenital heart disease by the National Institutes of Health.

Treatment of ACHD is based on the severity of the condition. Some patients require little treatment. Others may need to be treated with medications, invasive procedures or surgery. Most adults with congenital heart disease need to be monitored, take precautions and occasionally receive treatment throughout their lives.



Heart scientists discover protein that may be one cause of heart failure

Researchers at the Peter Munk Cardiac Centre have discovered a protein switch which can trigger a cascade of events leading to heart failure, pointing to a new direction for drug development.

“Our research suggests that PINK1 is an important switch that sets off a cascade of events affecting heart cell metabolism,” says Dr. Phyllis Billia, principal author and heart failure specialist at the Centre. “This could be one of the inciting events in the development of heart failure.”

The findings, published in *Proceedings of the National Academy of Sciences*, show that the absence of a certain protein, PINK1, causes heart cells to produce less energy. This lack of energy causes some heart cells to die, forcing the remaining cells to work harder to keep the heart going. In response to this stress, the heart muscle cells thicken, a condition known as hypertrophy.

Heart failure is the most common cause of hospitalization in North American adults, and over 50,000 are treated for advanced heart failure annually.

Transplantation is the only long-term treatment for end-stage heart failure patients and the long wait times for a matching donor organ make it necessary to find other alternatives.

“Heart failure remains a silent epidemic in North America, except for those who suffer from this devastating disease. Current therapies, while effective, only target the symptoms of heart failure,” says Dr. Vivek Rao, co-author of the study and Surgical Director of the Heart Transplant Program at the Centre. “The discovery of PINK1’s role in the development of heart failure may lead to novel treatment to prevent heart failure in those at risk. This discovery represents a novel and as yet, untapped mechanism to fight the battle against heart failure.”

In the lab, researchers “knocked-out” or genetically removed the PINK1 gene in mice and studied their heart cells under the microscope. They found that although the hearts initially develop normally, they begin to fail after two months, suggesting that PINK1 isn’t required for organ development; rather it is crucial

for protecting against heart failure. Until now, research into the PINK1 gene has focused on its links to early-onset Parkinson’s disease and certain cancers including esophageal and endometrial. This is the first study to establish its connection to heart disease.

While more research is required to develop potential clinical treatments, this discovery represents a new way of thinking about the involvement of certain proteins in the progression of heart failure.

“We need to learn more about PINK1 and the other proteins it interacts with at the sub-cellular level,” says Dr. Billia. “But if we’ve identified the inciting event that causes the chain of events leading to failure, research and drug development strategies should be focused in this new area of science.”

The research was financially supported by grants from the Canadian Institutes of Health Research.

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In the news

ART EXHIBIT TELLS STORIES OF HEART PATIENTS

Nursing Professor Jennifer Lapum in collaboration with Dr. Terry Yau, cardiovascular surgeon in the Peter Munk Cardiac Centre, is using art to humanize health care. Along with a team from Ryerson University, they created an exhibit, *The 7,024th Patient*, to portray the experiences of open-heart surgery patients.

"This project is different as it expresses the patient's point of view in a way that has never been done before," says Dr. Yau, who provided feedback to the design team from a surgeon's perspective. "It's the first time that anyone has talked to patients about their feelings and synthesized it into an artistic showcase using photography and poetry."

Professor Lapum, a former TGH ICU nurse, interviewed 16 patients, two to four days after surgery and then four to six weeks following discharge. Her main findings pointed to the need to enhance the delivery of a more humanistic approach to health care in which patients' unique attributes and the psychosocial are integrated into care.

"Often as a practitioner in heart surgery, it's easy to get so caught up in the technological routines that you almost forget it's a person in a hospital bed not just a patient," she adds. "I want people to feel the depth of trauma a patient undergoes because it's not just physical but emotional too."

"We as healthcare providers only have so much time to spend with our patients, but this exhibit really gives patients a voice," says Dr. Yau. "I hope the exhibit helps healthcare providers to become more sensitive to the patients' concerns, rather than what we as medical staff think their concerns are."

The 7,024th Patient
Stories of Open Heart Surgery and Recovery

Based on research that explored patients' narratives through interviews, this exhibition embodies their lived experiences in an intimate landscape of poetry and photography.

I count backwards
by the time I get to nine
I'm gone

Wednesday, June 15, 2011
8:00am to 9:00pm
Reception, lecture & reading at 3:30pm

Thursday, June 16, 2011
8:00am to 7:00pm

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DR. MANSOOR HUSAIN NAMED DIRECTOR OF TORONTO GENERAL RESEARCH INSTITUTE

Dr. Mansoor Husain, Senior Scientist at Toronto General Research Institute (TGRI), has been appointed as the new Director of TGRI. He replaces Dr. Richard Weisel, who is stepping down after six years.

As a specialist in cardiovascular disease and nuclear cardiology, Dr. Husain brings outstanding clinical and research credentials to the role. He is currently Director of Research at the Peter Munk Cardiac Centre and Director of the Heart & Stroke/Richard Lewar Centre of Excellence at the University of Toronto. In addition, he is affiliated with the McEwen Centre for Regenerative Medicine. Dr. Husain was awarded the Gold Medal in Medicine from the University of Alberta in 1986. His subsequent clinical and research training was completed at St. Michael's Hospital, UHN, MIT and Harvard Medical School.

For more information, please visit www.petermunkcardiaccentre.ca
To make a donation visit www.inaheartbeat.ca or call 416-340-4056

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