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THE BEAT™

A COMPENDIUM OF INFORMATION ABOUT THE UNIVERSITY OF OTTAWA HEART INSTITUTE

HIGHLIGHTS

"This [RAFT] will certainly change the approach of cardiovascular medicine in the way we treat mild to moderate cases of heart failure."

— Dr. David Birnie, Director, Pacemaker/Defibrillator Clinic, UOHI (from Combination Device Improves Survival for Heart Failure Patients, page 1)

It has been accepted among cardiac surgeons that surgery to repair severe mitral valve regurgitation should be performed when there is a better than 90 per cent chance of success. However, Dr. Mesana argues for a much higher rate.

(from A Case of Extreme Complexity: Mitral Valve Repair, page 2)

The anticipated availability of synthetic natriuretic peptides in coming years will greatly increase the therapeutic value of these hormones and has the potential to impact millions of people suffering from chronic heart failure and hypertension.

(from Celebrating 30 Years of the Endocrine Heart, page 5)

"Canada has a huge potential to be globally successful in medical device development if we put resources together from various institutes, hospitals, universities, and provinces."

— Tofy Mussivand, Director, Cardiovascular Devices Program, UOHI (from A Career of Translating Knowledge into Solutions, page 6)

IN THIS ISSUE

The Beat is published by the University of Ottawa Heart Institute (UOHI). Comments or questions about *The Beat* should be directed to Jacques Guérette, Vice President, Communications, at 613-761-4850 or jguerette@ottawaheart.ca. For more information about UOHI, please visit www.ottawaheart.ca.

Thirty years ago, Adolfo de Bold made the landmark discovery that the heart produces hormones. The field of research sparked by this finding has since generated nearly 27,000 scientific publications and important tests and therapies for heart failure patients. To mark the anniversary, the Heart Institute hosted a special symposium that brought together many of the world's leaders in cardiovascular endocrinology. See "Celebrating 30 Years of the Endocrine Heart" on page 5.

Combination Device Improves Survival for Heart Failure Patients

Dr. Anthony Tang and George Wells are the lead investigators of the RAFT clinical trial that showed cardiac resynchronization therapy improves survival in patients with less advanced heart failure.

"This is an important contribution to heart failure-related devices. A change of clinical practice guidelines can be anticipated."

– Dr. Clyde Yancy,
Past President of the American Heart Association

One of the largest, most extensive worldwide investigations into heart failure, led by the University of Ottawa Heart Institute, shows conclusively that a new therapeutic implant synchronizes and strengthens a fading heartbeat while reducing risk of death by 24 per cent compared to the current treatment.

The research, co-led by Dr. Anthony Tang and George Wells, PhD, at the Heart Institute, brings the promise of life-saving treatment for patients with symptoms of mild to moderate heart failure. Each year, more than 500,000 Canadians and 5 million Americans suffer heart failure. An increasingly common condition among an aging population, heart failure can lead to sudden cardiac death.

"This is an important contribution to heart failure-related devices," Dr. Clyde Yancy, Past President of the American Heart Association (AHA), told a plenary of the AHA Scientific Sessions in Chicago. "A change of clinical practice guidelines can be anticipated."

Currently, therapeutic implants are employed mainly for patients suffering serious heart failure. But this research was applied to patients with mild and moderate heart failure. Extending the use of implants provides an opportunity to improve care to a larger patient group, said Dr. Yancy.

Results of the clinical trial, which got under way in 2003, were published online in the prestigious *New England Journal of Medicine* and coincided with the release of the Heart Institute analysis at the conference. The research represents one of the largest international medical device trials, comprising 1,798 patients in 24 centres in Canada, Australia, Europe and Turkey.

"It was one of the longest-running trials and this will certainly change the approach of cardiovascular medicine in the way we treat mild to moderate cases of heart failure," said Heart Institute electrophysiologist Dr. David Birnie, Director of the Pacemaker/Defibrillator Clinic and a key member of the study team.

During the trial, heart failure patients were implanted with either a basic implantable cardioverter defibrillator (ICD) or with a new device carrying insulated wires called leads to transmit signals and electrical impulses to the heart in an effort to stimulate and coordinate the heart to beat in sync. This approach is called cardiac resynchronization therapy (CRT).

The study, which followed patients for an average of 40 months, showed that those receiving CRT lived longer with a reduction of the rate of death. In addition, patients with CRT were less likely to be admitted to hospital for worsening of heart failure.

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(Combination Device Improves Survival for Heart Failure Patients, continued)

Dr. David Birnie, Director of the Heart Institute Pacemaker/Defibrillator Clinic, holds one of the implantable devices that the RAFT trial showed to be of value for patients with mild and moderate heart failure. Dr. Birnie and his team recruited and followed 226 trial participants.

"This kind of device brings the potential to save thousands of lives in Canada alone and offers new hope to so many heart patients and their families. Helping the lower chambers of the heart beat strongly and in unison can improve a person's quality of life, keep them out of hospital longer and reduce their risk of sudden death," said Dr. Tang.

Until now, no research had been undertaken to examine the specific benefits and survival rates in heart failure patients who have been implanted with a CRT along with an ICD.

The largest drawback to the new therapy emerged in reports in the United States, which funds medical care differently from Canada. The main concern was the cost of the device and the implantation procedure, which is in the US$35,000 range there. But Dr. William T. Abraham, Chief of Cardiology at Ohio State University, was reportedly unperturbed by the cost, saying the costs would in no way "keep the floodgates closed" and the device would gain increased adoption because of the lower death rate among patients implanted with CRT.

It is estimated that 22 million people around the world have heart failure and the cost of caring for the disease in the U.S. alone is around the US$40 billion mark. One reason for the high cost is believed to rest on the fact that heart failure patients can quickly end up in the emergency ward and hospitalized after even a slight change in diet leads to fluid buildup in the lungs. Patients with reduced heart capacity tend to exhibit fluid buildup.

The lengthy study was funded by Medtronic of Canada Ltd. and the Canadian Institutes for Health Research. For more on the Heart Institute at AHA 2010, see page 7.

MORE INFORMATION ONLINE

Links in the electronic edition at www.ottawaheart.ca/thebeat/

- Read the *New England Journal* article
- See the webcast of Dr. Anthony Tang and George Wells presenting the findings
- Read about heart failure

UOHI at the Canadian Cardiovascular Congress

The Canadian Cardiovascular Congress (CCC) landed in Montreal this year for five days of presentations, symposia and networking. From October 23–27, the cardiovascular community came together for the largest such event in Canada. Total Heart Institute program items approached 100 again in 2010, and as Chair of the Canadian Cardiovascular Society's portion of the conference, our own Dr. Rob Beanlands helped to shape the event.

The following stories illustrate several areas of special interest—from basic research to surgery to nursing—as well as some conference highlights. Check out the full Heart Institute CCC program guide at: www.ottawaheart.ca/thebeat/.

UOHI AT CCC 2010

A Case of Extreme Complexity: Mitral Valve Repair

Dr. Thierry Mesana

The valve is the gateway to the chambers of the heart, and valve disease has serious implications. Sometimes, heart valve disease does not cause any symptoms. When symptoms do occur, they can be confused with the effects of aging or physical inactivity. Such cases prove difficult for cardiologists and surgeons, who must evaluate the need for surgery.

The issue of asymptomatic (without symptoms) severe mitral valve degeneration is a controversial one in cardiac surgery. Whether or not to operate is an ongoing debate, and in some centres, the decision can be made to simply treat a patient with medication while continuing observation until surgery is warranted.

One reason to forgo surgery rests largely on the complexity of severe degenerative mitral valve repair—a surgical procedure that requires a combination of considerable dexterity and experience. Dr. Thierry Mesana, Chief of Cardiac Surgery at the Heart Institute, is considered one of the world's leading experts in mitral valve repair. He currently performs about 150 such surgeries a year.

A workshop at the Canadian Cardiovascular Congress was filled to a near overflow capacity of 200 mainly cardiologists and cardiac surgeons, who came to hear their peers debate the case for or against surgery.

Roughly 2 per cent of the population suffers mitral valve regurgitation. The condition is caused by a faulty valve flap, called a prolapse. It can cause a variety of complications, such as blood leaking backward, heart infection, an enlarged heart and heart failure.

Because specific surgical procedures differ from one patient to the next—repairs are highly specific to the unique case at hand—patients should generally be referred to centres with higher volumes of mitral valve repair. These centres of excellence would play a significant role in the positive outcomes of such a complex surgical technique.

It has been accepted among cardiac surgeons that surgery to repair severe mitral valve regurgitation should be performed when there is a better than 90 per cent chance of success. However, Dr. Mesana argues for a much higher rate, that the bare minimum must be 95 per cent and higher.

One important contribution to success, is the use of transesophageal echocardiography (TEE). Three-dimensional TEE is an emerging technique that gives surgical teams real-time feedback on the success of procedures such as valve repair. The Heart Institute is home to several of the country's leaders in three-dimensional TEE.

The timing of surgery in patients with asymptomatic mitral regurgitation has been especially controversial because of the different causes of valve dysfunction and the lack of a precise measure of disease severity. TEE goes a long way to solving part of the dilemma. A surgeon needs a perfect image of the area to assess the technique necessary for any particular repair.

Some surgeons have argued in published papers that asymptomatic patients with severe degenerative mitral regurgitation can be safely followed until either symptoms occur

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How TEE Works

Echocardiography, the use of non-invasive ultrasound to picture the heart's structure and function, is a mainstay of cardiac diagnosis and monitoring. Traditionally, echocardiography has been performed transthoracically, meaning that external probes image the heart via ultrasound waves transmitted through the chest wall.

Transesophageal echocardiography (TEE) takes advantage of the fact that the heart lies close to the esophagus, the pathway that carries food from the mouth to the stomach.

TEE uses a small probe on the end of a flexible line that can be threaded down the patient's esophagus, imaging the heart from its back side. Without the chest wall, ribs and lungs in the way, TEE provides a better picture of the heart, and the procedure can be carried out during surgery.

(A Case of Extreme Complexity: Mitral Valve Repair, continued)

or until serious problems with the left ventricle kick in. Further complicating the picture is that the severity of symptoms does not always correlate with the severity of the heart valve disease. It is known that some people with mild symptoms, for example, may need treatment immediately to prevent further heart damage.

At the Heart Institute, severe degenerative mitral valve repair is regarded as the best option for nearly all patients with a leaking mitral valve and for many with a narrowed (stenotic) mitral valve.

Compared to valve replacement, for example, Dr. Mesana believes that mitral valve repair provides better long-term survival, improved preservation of heart function, lower risk of complications and often elimination of long-term use of blood thinners.

A major portion of his address was given over to a demonstration of a dozen surgical techniques for mitral valve repair. This was Dr. Mesana's graphic lesson on how there is no single approach to surgical repair and why experience combined with a deft pair of hands are important contributors to success.

UOHI AT CCC 2010

Smoking Cessation

Dr. Andrew Pipe, Chief of Prevention and Rehabilitation at the Heart Institute and a widely recognized advocate for smoking cessation, presented the Canadian Cardiovascular Society's first ever official statement on tobacco use. Also, he received that society's Award of Merit for significant contributions to disease prevention and health promotion.

The name Dr. Andrew Pipe, Chief of Prevention and Rehabilitation at the Heart Institute, is synonymous with smoking cessation in Canada. When the Canadian Cardiovascular Society (CCS) developed a position statement on the topic, it is little surprise that Dr. Pipe was chosen to co-chair its development.

What does come as a surprise, as Dr. Pipe made clear in his presentation, is that this was the first official statement on tobacco use by CCS. This absence of an official stance is remarkable given the dramatic health benefits to quitting. Two years after quitting, the risk of heart attack or stroke drops by 50 per cent.

The CCS position statement consists of six elements:

1. Provide standard smoking interventions in a systematic way
2. Identify and document the smoking status of patients
3. Provide clear, non-judgmental advice
4. Become familiar with available drug therapies
5. Educate trainees in appropriate management
6. Advocate for public policies to control tobacco products

Dr. Pipe also presented an exploratory study this year into the relative effectiveness of methods for nicotine replacement therapy (NRT). NRT is an intervention offered to heart disease patients at the time of hospitalization, consistent with the Heart Institute's Ottawa Model for Smoking Cessation.

The Heart Institute uses several options, which include a nicotine patch, bupropion and varenicline. All are proven to increase the likelihood of smoking cessation. However, varenicline and bupropion have been singled out by the United States Food and Drug Administration as contributing to mood disorders in some users, and the agency is requiring new safety packaging. Their use is carefully monitored at the Heart Institute.

The Prevention and Rehabilitation group conducted a pilot randomized trial of smokers who were selected to use either varenicline or the nicotine patch for 12 weeks. All participants received 20 minutes of counselling by a nurse who came to their bedsides in hospital. Other materials and regular phone calls were provided after discharge.

Preliminary results showed 45 per cent of patients who used varenicline remained smoke-free compared to 32 per cent in the nicotine patch group. The data indicate the need for a full-scale comparative trial so that effectiveness can be weighed against potential side effects when making clinical decisions.

UOHI AT CCC 2010

Improving Quality of Life in Old Age

Dr. Marc Ruel

As the elderly population continues to grow in Canada and elsewhere, advances in medical technology provide an increasing array of treatment options designed to improve quality of life in severely ailing heart patients.

Aortic stenosis is an increasingly common condition among the elderly, where narrowing of the aortic value dramatically reduces blood flow from the heart's left ventricle to the rest of the body.

An estimated 188,000 Canadians suffer from severe aortic stenosis. Until recently, the only treatment available was open-heart surgery to remove and replace the diseased valve. Because of the advanced age of patients and their accompanying conditions, such surgery can be high risk, if not out of the question. A new approach for treating these patients is the minimally invasive insertion of an aortic valve stent. A full workshop at the Canadian Cardiovascular Congress was dedicated to issues surrounding development and implementation of this catheter-based procedure.

At the Heart Institute, most of these patients are in their 80s and even 90s. Because they are largely considered at higher risk, a special committee discusses the value of each case individually. The recommendations are documented, meticulously charted and relayed to the patient as well as to the referring physician.

Two types of aortic valve stents are available for the procedure, known as transcatheter aortic valve implantation (TAVI). One is the Edwards Sapien; the other, used at the Heart Institute, is the Medtronic CoreValve.

Increasingly, cardiac units are examining the new option of TAVI. At the Heart Institute, interventional cardiologist Dr. Marino Labinaz partners with cardiac surgeon Dr. Marc Ruel to perform this procedure in a collaboration not common at other cardiac centres.

Dr. Ruel explained the surgeon's perspective at the Congress workshop, describing the procedure, the CoreValve and the team considerations for TAVI. He used the word "operators" to describe the exceptional team approach in manoeuvring the aortic stent into place via the catheter. The catheter carries the small netted stent that is implanted to serve as the new valve and restore normal function to the heart.

As Dr. Ruel noted, tasks are divided between the two "operators"—the surgeon and the cardiologist. One positions the balloon carried in the catheter, which is threaded to the heart, while the other expands the balloon wide enough to hold the stent.

"Cardiologists and surgeons bring different skill sets," said Dr. Ruel. "While a cardiologist's background involves more experience and facility with wires and fluoroscopic imaging, a surgeon's background involves a better knowledge of the aortic-root anatomy and of open vascular approaches."

More important, he said, the team is unusually well positioned to provide a wide technical competency, as well as collaborative and unbiased opinion regarding the use of this new technology—which, he carefully noted, is not yet completely proven.

As a result, a Heart Institute Committee for High-Risk Patients with Aortic Valve Disease was created with at least two surgeons and two cardiologists. One surgeon and one cardiologist are not involved in transcatheter valves and are considered internationally recognized surgical and echocardiographic valve experts. All patients considered for the implantation are assessed in this venue.

There are some logistical difficulties in bringing together a committee to review all the cases and with having two different physicians perform each procedure, Dr. Ruel explained. But the different sets of skills enable more objective recommendations and ensures a wide scope of technical knowledge. Further, this model provides strong credibility for a solid TAVI program.

These multidisciplinary collaborative teams may well become institutional or governing-body requirements in the future for application of new treatments, such as TAVI and others yet to be developed.

UOHI AT CCC 2010

Awards

Two Heart Institute physicians were honoured this year with special awards from CCS. The annual awards celebrate contributions to the field of cardiovascular medicine in various categories. Dr. Martin Green, Director of the Electrophysiology and Arrhythmia Fellowship program, received the Distinguished Teacher Award. Dr. Green received the award in recognition of his long-time commitment to educating and inspiring trainee physicians.

Dr. Andrew Pipe received the Dr. Harold N. Segall Award of Merit. This award is presented for significant contributions "to the prevention of cardiovascular disease or the promotion of cardiovascular health." While Dr. Pipe is also known for his promotion of physical fitness and sport, he was selected for spearheading the development of the Ottawa Model for Smoking Cessation and his outspoken advocacy for systematic approaches to quitting smoking. The Ottawa Model has been implemented in more than 70 centres across Canada.

UOHI AT CCC 2010

Regenerative Medicine


Erik Suuronen

Following a heart attack, cardiac tissue is damaged by lack of oxygen, known as ischemia. The heart has a maintenance system for replacing cells that regularly die off, but the amount of damage caused by a heart attack overwhelms that system. The search for ways to enhance or augment the body's natural repair mechanisms has become a highly active area of research. This is particularly true at the Heart Institute where fully 10 per cent of UOHI presentations at CCC were associated with regenerative medicine.

The general idea behind regenerative therapies for cardiac repair is to deliver undifferentiated cells—stem or progenitor cells—to the damaged site where they will become new heart muscle or blood vessels to supply nutrients to the growing tissue. While this sounds relatively straightforward, developing successful approaches is a complex undertaking.

Most of this research is coming from the labs of two investigators and collaborators: Dr. Marc Ruel, surgeon and Director of the Cardiac Surgery Laboratory, and Erik Suuronen, PhD, Director of the Cardiovascular Tissue Engineering Laboratory.

A major issue in developing cell-based therapies has been getting introduced cells to adhere at target sites and, once attached, keeping them alive long enough so that they can differentiate and form new tissue. The researchers have had success using an injectable collagen-based material that gels at body temperature. The material acts as a scaffold that undifferentiated cells can cling to. Adding certain molecules to the material attracts cells to the site and helps them thrive.

Several CCC presentations addressed refinements to this technique. Others looked at the use of ultrasound to guide the injection of cells to target sites and at new ways to track the progress and impact of introduced cells. The ability to track therapeutic cells over time in a non-invasive fashion is highly valuable for measuring the success and understanding the failure of different approaches. The researchers are working closely with the Heart Institute's imaging group to develop new methods using PET scans.

UOHI AT CCC 2010

Medical Care for Advanced Surgical Techniques

Tell coronary bypass patients five years ago that someday they would be rolled into their hospital rooms by wheelchair after surgery and they might be more than a little skeptical.

Today, that is exactly the scenario at the Heart Institute for patients who have undergone a keyhole surgical procedure to replace up to three blocked arteries. Since mid-2009, this minimally invasive method has been performed on a closed chest—rather than cutting open the breastbone—in at least 50 patients.

The benefits in terms of recovery for these patients are astounding. With a shorter healing time, they can return to near normal activities much more quickly and with fewer complications. The merits of this kind of procedure, however, extend from the hospital bed, along the corridor of a cardiac care ward, to the nursing station and beyond. Hospital stay is significantly reduced, decreasing hospital care and costs by 15 to 35 per cent. A normal five- to seven-day stay is cut to four and possibly three days for some patients. At roughly $2,000 per day per bed, the savings are substantial.

At the Heart Institute, cardiac nursing care—especially post-surgery—largely entails one-on-one monitoring and constant vigilance for bleeding, infection and any untoward event. For patients who are returned to their hospital beds after undergoing multi-vessel small thoracotomy (MVST) coronary artery bypass grafting, nurses remain no less vigilant. Yet the medical care is significantly altered in a new age of advanced surgical practice.

"The biggest issue facing these patients is that they don't look like a typical surgery patient," said Fiona MacDonald, a Heart Institute cardiac care nurse. Many don't even believe they feel like a typical surgery patient. They can begin walking short distances with physiotherapy and have a limited ability to move their arms on the first day after surgery.

However, these patients soon learn that pain and fatigue are quick to set in, explained MacDonald, part of a Heart Institute cardiac nursing team that explained to the Canadian Cardiovascular Congress how MVST differs dramatically from traditional surgery in post-surgical medical care.


Minimally invasive bypass surgery is much less debilitating for patients than traditional procedures that open the chest cavity. The small incisions are circled above. Fiona MacDonald told nurses at CCC that, while recovery is much improved, patients need to be reminded that they have had heart surgery and must not try to do too much too soon.

TRADITIONAL CORONARY BYPASS VS. MINIMALLY INVASIVE SURGERY

CABG	MVST
Sternotomy, or opening the breast bone	Small lateral incision 4 to 6 cm (1.5 to 2.5 inches)
Heart and lung machine used while the heart is essentially shut down for surgical repair	Generally, no chest tubes
One or more incision sites of about 20 cm (8 inches)	No other incision sites
Pacemaker wires to help the heart maintain its rhythm are used to prevent arrhythmias and ensure a good heart rate	Generally, pacing wire needed only at the incision site, if at all
Chest tubes to drain blood from around the heart	Less operative bleeding

"MVST patients often come up from the operating theatre after surgery in a wheelchair and do not look much like they have had an operation," she continued. "This can be a problem because without the big incision, they need to be reminded that they have had cardiac surgery. They have a very small incision that is covered with a simple dry dressing."

There are a number of differences (see chart) between traditional coronary artery bypass grafting (CABG) and MVST, which is performed on a select group of patients. Ideal MVST patients are generally younger males, with a normal body mass index, tall and thin, and considered to be otherwise healthy individuals. That is, they are not diabetic and have no major accompanying illnesses.

Traditional CABG patients are wheeled by gurney from the operating theatre into the Cardiac Surgery Intensive Care Unit, where they are carefully monitored and pain is managed initially by a morphine drip. Complications, including atrial fibrillation—an irregular heartbeat, are not uncommon.

Recovery can be a challenge. Resumption of movement and walking is a slow process. No lifting is possible for several weeks. Dressings are larger and require frequent changes to check for and prevent infection.

MVST patients are a much different breed. Fewer dressings are needed, infection is virtually zero and fewer blood products, such as transfusions, are needed because there is less blood loss during the surgical procedure.

"Pain and breathlessness are still major issues for these patients," said MacDonald, because of the swelling around the site where the unique clamps are set to open a small access channel to the heart. "In the end, an MVST allows nurses to get the patient up sooner and out the door more quickly."

MVST is still considered a leading-edge procedure available only for suitable candidates. The traditional approach is regarded as standard practice for many patients because they often have other illnesses, such as diabetes and kidney problems, that are taken into account.

An estimated 630 CABGs are performed each year at the Heart Institute. CABG represents about 80 per cent of surgical cases both in Ottawa and throughout North America.

Celebrating 30 Years of the Endocrine Heart

"The Endocrine Heart: 30 Years Later" brought together leading scientists in cardiovascular endocrinology from around the world to speak on the current state of knowledge and expected directions for new therapies.

Thirty-one years ago, it was not known that the heart produces hormones. That changed in 1981 when Adolfo de Bold, PhD, discovered that muscle cells in the atria of the heart secrete atrial natriuretic factor (ANF), an essential hormone that regulates fluid volume, blood pressure and sodium. Since that watershed discovery, thousands of scientific papers have been published on cardiovascular endocrinology, and related diagnostic and therapeutic tools have been developed.

On September 23 and 24, the University of Ottawa Heart Institute hosted "The Endocrine Heart: 30 Years Later," an international symposium to celebrate de Bold's achievement and look at the past, present and future of cardiovascular endocrinology. Held in association with the International Society of Hypertension, the event brought together leading scientists from as far away as Brazil, Japan and New Zealand.

> Prior to the discovery of cardiac endocrine function, the heart was considered a passive pump, simply pushing blood through the body as directed by the brain stem.

Prior to the discovery of cardiac endocrine function, the heart was considered what amounts to a passive pump, simply pushing blood through the body as directed by the brain stem. It was not thought to exert hormonal control over the cardiovascular or other body systems.

In that intellectual climate, de Bold's chosen area of research was considered unfashionable, and funding did not flow easily. The discovery of ANF was the culmination of 12 years of painstaking bench work with a laboratory staff that consisted primarily of de Bold himself; his wife, Mercedes; and a technician.

ANF turned out to be the first in an entirely new family of hormones, the cardiac natriuretic peptides, which also includes brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). These cardiac hormones play an important role in blood pressure regulation and the growth of heart tissue, and they have been shown to impact most known biological functions. Their relationship to heart failure and inflammation makes them attractive targets for research into the treatment of heart disease.

As one speaker at the "Endocrine Heart" symposium made clear, de Bold's tenacity was inspirational. Benoit Bruneau pursues questions of cardiac development at the Gladstone Institute and the University of California, San Francisco. He received his PhD under de Bold and lauded him as a mentor. De Bold, he said, provided a good model of what it is to be a scientist, by encouraging his students to think critically, to ask the right questions and, importantly, to pursue them.

The core of the symposium focused on what we have come to know about the genetics and molecular pathways involved in the function of cardiac natriuretic peptides, as well as their impacts on the cardiovascular system.

The Heart Institute's own Dr. Michael Gollob and Dr. Haissam Haddad discussed the broad relevance of ANF to the clinical setting. Dr. Gollob, Director of the Inherited Arrhythmia Clinic and the

(continued on page 6)

UOHI AT CCC 2010

How Far We Have Come

A crowded session entitled "Evolution in Medical Therapies" offered an interesting look back at the past 10 years to see how care has changed in a number of cardiovascular disease areas. Several of the presentations touched on work associated with the University of Ottawa Heart Institute.

In terms of atherosclerosis, statin drugs, which reduce LDL cholesterol levels, have become the keystone of treatment. Efforts to develop drugs that increase HDL cholesterol levels have so far been ineffective in humans despite positive studies in animals. This will be a focus of research in the coming decade, as will the development of anti-inflammatory drugs. Atherosclerosis is a chronic inflammation disease, and new drugs in trial have shown reductions in plaque and in markers of systemic inflammation.

Holes still exist in our understanding of the relationship between the extent of plaque development and subsequent cardiac events. The Canadian Atherosclerosis Imaging Network (CAIN) is a national network that will conduct imaging studies using all relevant modes of imaging at a number of sites across the country. The Heart Institute helped to establish this effort—unique in the world—to integrate atherosclerosis imaging data with genetic, pharmacogenomic, biomarker, proteomic and metabolomic data.

For adult congenital heart disease (ACHD), a comparison was made between the state of affairs in Canada with that of the United States. ACHD is a growing area of care, with adult patients recently outnumbering children for the first time as a result of improved survival rates and longevity. Due to the nature of the U.S. health care system, the rate of monitoring of ACHD patients is quite low. Only 5 per cent are in ongoing care, and most come to light only following a cardiac event.

In Canada, the situation is much better thanks in large part to our centralized system, which facilitates the tracking of patients throughout their lives. Credit also goes to the Canadian Adult Congenital Heart Network, which provides coordination across 15 clinics nationally. Dr. Luc Beauchesne, Director of the Heart Institute's Adult Congenital Heart Clinic, presented the first ever survey of these clinics at the American Heart Association's Scientific Sessions in 2008. Those findings showed that, while Canada is well ahead of the U.S. in providing ongoing care, there are areas in need of improvement. These include improving wait times and providing more consistent support across the network of clinics.

Heart failure is another area with increasing patient numbers. Generally a disease of the elderly, the incidence of heart failure is rising along with the average age of the population. In 1999, ACE inhibitors and beta blockers were the major advances in therapy. In 2010, cell therapy looks to be the next possible breakthrough. The addition of angiotensin receptor blockers (ARBs) to the drug arsenal has continued improvement of all-cause death in heart failure patients. Implantable cardioverter-defibrillators and pacemakers have also been important contributors to survival in patients with advanced heart failure.

Another new therapy that is about to be assessed in a clinical trial is a drug that combines an ARB with the ability to extend the duration of natriuretic peptide activity. This work would not have been possible without the discovery of the first natriuretic peptide by long-time Heart Institute investigator Adolfo de Bold. (For more information on natriuretic peptides and their discovery, see "Celebrating 30 Years of the Endocrine Heart" above.)

Arrhythmia management and sudden cardiac death (SCD) were also discussed. In 2000, SCD and atrial fibrillation were poorly handled. The development of various cardiac ablation approaches (surgical, radio frequency, cryoablation) has made it possible to treat a large segment of atrial fibrillation cases. These procedures scar certain sites in the heart, preventing them from conducting errant electrical signals. Prevention of SCD has been less successful. Much progress has been made with single gene genetic disorders that cause potentially lethal arrhythmias. Heart Institute President Dr. Robert Roberts has been a leading figure in this area. Still, these disorders affect only a small percentage of the population. Heart attack survivors have high rates of SCD. The use of pacemakers reduces this risk and optimization of heart pacing has progressed a great deal. We now know that pacing of the right ventricle is not the way to go and that the less pacing used, the better.

In all, the session provided an excellent reminder of how far the treatment of heart disease has come in the past decade. It also made clear how much we have left to do in our collective mission of eliminating the number one killer in North America.

(Celebrating 30 Years of the Endocrine Heart, continued)

Genetics of Cardiac Arrhythmias Research Laboratory, spoke on the connection between ANF and atrial fibrillation, the most common cardiac arrhythmia.

Like atrial fibrillation, heart failure is a growing problem in an aging population. Associated health care costs are $4 billion annually in Canada. Dr. Haddad, Director of the Heart Failure Program and Medical Director of Transplantation, discussed the role of ANF and BNP in the clinical management of heart failure. Measurement of circulating BNP is a common diagnostic tool for the condition. As Dr. Haddad reported, ANF and BNP are independent markers of heart failure, they are strongly predictive of death and, used alone, they are as good or better than physical exam of the patient for diagnostic purposes.

Many presenters focused on potential diagnostic and therapeutic applications of the natriuretic peptides. Dr. John Burnett of the Mayo Clinic described his work on the use of ANF and BNP in treating heart failure. No new drugs for heart failure have come through the development pipeline in more than 10 years, even as the elderly population continues to grow. ANP and BNP are currently used to treat acute heart failure, since they have significant protective (anti-cell death) and regenerative properties. However, the natural hormones have a very short half-life—a matter of minutes—within the body.

Dr. Burnett is working on developing synthetic versions that would not promote the unwanted side effect of excessively low blood pressure and would have longer-lasting positive effects. Since these synthetic compounds mimic natural peptides, they should be safe and effective, he told the audience. Currently, his research group has one synthetic peptide in human studies and is conducting other research into using ANP therapy after a heart attack to prevent heart failure. They are also looking at CNP to prevent fibrosis in cardiac tissue. "None of this would be possible," he said, "without Adolfo's work."

The de Bold lab is also actively pursuing synthetic therapeutic analogs of ANF to create compounds that could stimulate regeneration of the heart tissue for days instead of minutes. Such compounds could have clinical applications for the treatment of acute heart failure and heart-tissue repair after a heart attack. To date, they have filed one patent application for a promising compound that genetically fuses ANF to human serum albumin, which extends its time in the bloodstream by more than 70-fold.

> "De Bold provided a good model of what it is to be a scientist, by encouraging his students to think critically, to ask the right questions and, importantly, to pursue them."
>
> – Benoit Bruneau, PhD,
> Gladstone Institute and the University of California, San Francisco

De Bold and his colleagues are also working to understand the factors that control BNP gene expression, since the hormone appears to play an important role in remodeling heart muscle under chronically stressful conditions, such as high blood pressure or inflammation. They are also examining how the biophysical forces that expand and contract the heart muscle affect the secretion of ANF and BNP.

Even after more than 40 years at the bench, de Bold remains enthusiastic about the opportunities to continue harnessing the endocrine function of the heart to improve the treatment of cardiac disease. He thanked the symposium participants for their dedication to a field of research that only emerged three decades ago.

"Probably the greatest honour in life is to have your achievements recognized by your friends and colleagues. It is quite a privilege to have this event organized in recognition of the work we have done," he told the audience.

In scientific terms, the importance of the ANF discovery is reflected in the nearly 27,000 articles indexed in PubMed on the subject. By extension, tens of thousands of researchers have found ANF and related hormones a subject worth investigating. Clinically, the anticipated availability of synthetic natriuretic peptides in coming years will greatly increase the therapeutic value of these hormones and has the potential to impact millions of people suffering from chronic heart failure and hypertension.

MORE INFORMATION ONLINE

Links in the electronic edition at www.ottawaheart.ca/thebeat/

- See the Cardiovascular Endocrinology Laboratory page
- Read an earlier profile of Adolfo de Bold from *The Beat*

A Career of Translating Knowledge into Solutions

Tofy Mussivand, Director of the Heart Institute's Cardiovascular Devices Program, was honoured in November with the Knowledge Translation Award from the Canadian Institutes of Health Research. His career has been devoted to the development of innovative medical devices and the education of future biomedical engineers.

> "It takes work across different disciplines in order to come up with practical solutions to complex health issues."
>
> – Tofy Mussivand,
> Director, Cardiovascular Devices Program, UOHI

On November 16 at the National Gallery of Canada, Tofy Mussivand, Director of the University of Ottawa Heart Institute's Cardiovascular Devices Program, received one of Canada's most prestigious medical awards: the Knowledge Translation Award from the Canadian Institutes of Health Research (CIHR). This award honours and supports outstanding contributions to the health of Canadians or to the health system through exemplary knowledge translation. The nomination came from several prominent scientists in Canada and the United States who are familiar with the engineer's achievements.

Mussivand has a long history of reaching across disciplines to solve difficult medical engineering problems. It's this willingness to collaborate and integrate knowledge from diverse areas of research that has been his hallmark.

"There is no single person or agency—or institute, university or hospital—anywhere in the world that has all the skill and resources needed to tackle complex health issues and come up with effective solutions. We all need each other," said Mussivand. "It takes work across different disciplines in order to come up with what I call practical solutions to complex health issues."

The CIHR award comes with a $100,000 grant that Mussivand plans to use to advance technologies, including two of the projects his group has in development. One is thermal (heat) therapy for the treatment of heart failure, which may help stimulate the body's natural healing mechanisms. A randomized, double-blind trial of the group's non-invasive thermal therapy system is planned.

Another ongoing project takes medical device technology into the nanoscale realm for the extraction of DNA from non-invasive biosamples, such as human fingerprints. "We wanted a way to get DNA quickly, inexpensively and non-invasively, and in order to do that, we needed several technologies and information that we didn't have," said Mussivand.

Through collaboration, "I found out we could combine nanotechnology with enzymes that naturally occur in our bodies, and that made what I was trying to achieve very simple, very doable," he continued. "Again, this shows that no single person is capable of having all the background knowledge needed to come up with a solution."

In addition to his research, Mussivand remains committed to training students in the lab and through the biomedical engineering degree programs he was instrumental in establishing at the University of Ottawa and Carleton University. "Canada has a huge potential to be globally successful in medical device development if we put resources together from various institutes, hospitals, universities and provinces," he explained. "What is necessary is to create the Canadian workforce required for such an endeavour."

MORE INFORMATION ONLINE

Links in the electronic edition at www.ottawaheart.ca/thebeat/

- See the Cardiovascular Devices Research Program page

The Beat Is Now Interactive

It is, perhaps, a major understatement to note the rapid and wide-spread interest in digital content as the world moves more toward electronic information and increasingly away from traditional print materials. This is fueling debate in many organizations as to when and how to divest from print and invest in digital.

Here at the Heart Institute, we feel the real issue is not about forcing the reader to pick one medium over another but about enhancing access and choice. For that reason, we will continue to deliver *The Beat* in both print and electronic forms for the foreseeable future. You choose the format you would like to read.

The new electronic edition of The Beat is fully interactive, with live links, an active table of contents and many other options to let you explore stories in greater depth.

At the same time, we do recognize the world is changing. To that end, we are pleased to be launching a new interactive edition of *The Beat* for our online readers. This issue of *The Beat* is the first to feature the new interactive edition. In technological terms, it is a major advancement over the PDF copies that were previously offered.

The interactive edition is, well, highly interactive, and it offers easy access to additional content relating to the stories you are reading. Almost everything in the edition is "clickable"—photos, diagrams, web site links, text and more—and you can use this interactivity to get additional details about a physician or researcher, a lab or department; to explore related research; to jump to a related web site, and more.

The interactive edition also has many easy-to-use features, such as a search function, a zoom function to enlarge or reduce text, and a variety of ways to turn pages (so as to emulate reading a print copy).

Going forward, we will continue to develop all versions of *The Beat* in order to bring you the latest news and developments from the Heart Institute. Try out the interactive edition and let us know what you think. You can email me at jguerette@ottawaheart.ca.

To get to the interactive edition, go to www.ottawaheart.ca/thebeat/

Jacques Guerette
Vice President, Communications

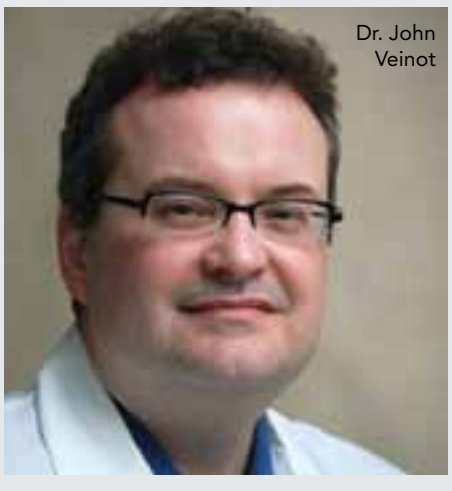
The Heart Institute at AHA 2010

The American Heart Association Scientific Sessions drew thousands of cardiovascular medical professionals from all over the world to Chicago this year. At the November conference, the University of Ottawa Heart Institute continued to expand its presence with 35 invited talks and oral and poster presentations.

One of the major highlights of this year's meeting was the presentation of the Heart Institute-led RAFT clinical trial. This study of heart failure therapy has since received much attention worldwide. For more on RAFT, see the story on page 1.

UOHI AT AHA 2010

Cardiac Biopsy


Dr. John Veinot

The pathologist's analysis of biopsied heart tissue is a key tool for diagnosing many conditions, assessing the severity of disease, and determining and tracking the course of treatment. A special session on cardiac biopsy was the first AHA session dedicated to pathology in many years. It offered a large audience of clinicians a primer/review of the role and value of cardiac pathology.

Among the speakers from Europe and North America was Dr. John Veinot, Director of Anatomical Pathology and a clinical investigator at the Heart Institute, as well as President-elect of the Society for Cardiovascular Pathology. He provided the big picture overview of what cardiac biopsy, known as endomyocardial biopsy (EMB), can do to aid clinicians in their decision making.

Pathologists can examine the structure and function of cardiac tissue using an array of techniques that include microscopy, tissue staining and labeling, and molecular analyses. These techniques can be brought to bear on a whole range of conditions, clarifying both the cause and next steps.

Myocarditis, infection of the heart, can be caused by multiple infectious agents that require different approaches to treatment. EMB can diagnose myocarditis and identify the type of infection, as well as track the course of treatment. The use of imaging can help to target biopsy sites and ensure that affected tissue is sampled.

Cardiomyopathy, or enlargement of the heart, can have many forms and causes. Some appear identical under standard microscopy, so additional tests can be necessary for proper diagnosis. EMB can also identify cardiac malignancies and can track rejection in heart transplant patients. In addition, it is an important tool for diagnosing certain rhythm disorders where the results of electrophysiology tests can be mimicked by other conditions.

Cardiac biopsy does have its limitations and downsides. These include invasiveness, turnaround time and cost. As Dr. Veinot emphasized, clinicians and pathologists need to function as a team in order to provide the best diagnostic and care options to their patients.

> Clinicians and pathologists need to function as a team in order to provide the best diagnostic and care options to their patients.

MORE INFORMATION ONLINE

Links in the electronic edition at www.ottawaheart.ca/thebeat/

- Read more about cardiac pathology

UOHI AT AHA 2010

New Findings in Cardiovascular Genetics

Genome-wide association studies (GWAS) use large population sets to identify genes associated with the likelihood of or protection against a particular condition. Given the number of samples required to achieve statistically significant results, researchers often form consortia to pool data. The Heart Institute genetics group has led and participated in many discoveries using this approach.

Alexandre Stewart, an investigator with the Ruddy Canadian Cardiovascular Genetics Centre, presented a Heart Institute-led effort that resulted in the discovery of a rare genetic variant that protects against coronary artery disease (CAD). This variant occurs in around 1.5 per cent of the general population. Rare variants are often missed in GWAS because the threshold for statistical significance is so high. The Heart Institute team tried scanning data sets for variants using a lower threshold, and it was successful. The finding has been confirmed in a second population grouping.

Other studies from consortia with Heart Institute participation presented research on the connection between CAD and heart attack. One tried to understand why many people who develop CAD don't experience heart attacks. They found indications that predisposition for arterial plaques to rupture—the primary cause of heart attack—may be controlled through genetic pathways independent of those controlling the development of the plaques in the first place. This result points to possible new targets for drug therapy. Another study found a new genetic variant associated with protection from heart attack seemingly due to increased arterial plaque stability.

MORE INFORMATION ONLINE

Links in the electronic edition at www.ottawaheart.ca/thebeat/

- Read about the Ruddy Canadian Cardiovascular Genetics Centre

UOHI AT AHA 2010

Potential Atherosclerosis Treatment Target

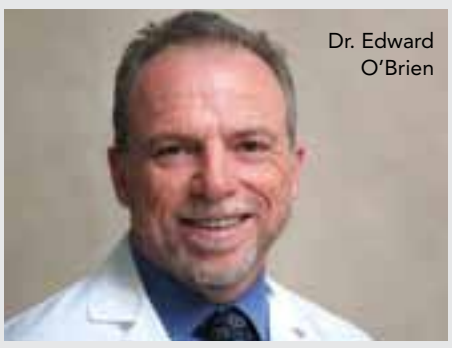

Lyne Sleiman

A growing body of research is examining the development and cellular mechanisms that inhibit atherosclerosis—the narrowing and hardening of the arteries as they become clogged with fatty plaques that can lead to heart attack. Molecular researchers at the Heart Institute have been investigating the role of one particular protein, known as cIAP2, and how it works to reduce the development of atherosclerosis.

Graduate student Lyne Sleiman and her team have analyzed the importance of cIAP2 in mouse models. Their research has shown that absence of cIAP2 in certain cells can protect mice from the buildup of plaques. This could point to cIAP2 as a target for therapy in the treatment and prevention of atherosclerosis. In addition to the presentation at AHA, Sleiman's work in this area landed her a finalist position for the student presentation award at the Canadian Cardiovascular Congress a few weeks earlier and Top Rated Abstract recognition at the AHA Arteriosclerosis, Thrombosis and Vascular Biology conference.

UOHI AT AHA 2010

Obesity in the Cath Lab


Dr. Edward O'Brien

Analysis showed that 87 per cent of patients were able to return home within 24 hours.

The growing population of obese patients is nowhere more evident than in cardiac care centres where the link between excess weight and cardiovascular disease is seen every day. To improve the safety of cardiac catheterization procedures on these patients, cardiologists at the Heart Institute employ a slightly different technique than is standard.

Since 1997, cardiologist Dr. Edward O'Brien has been performing cardiac catheterization to open blocked arteries in obese patients by inserting a catheter through an artery in the wrist (the radial artery) rather than through the traditional site in the groin.

Early results of research at the Heart Institute show this method reduces complications in heart patients who are considered severely obese, with a body mass index (BMI) at 40 or greater. BMI is a formula used to determine body fat. Normal BMI falls within the 18 to 24.9 range. Obese people have a BMI of more than 30.

Dr. O'Brien told an audience at the Scientific Sessions that sometimes the symptoms of cardiovascular disease are difficult to identify in the extremely obese. Some patients, weighing 400 pounds or more, cannot even fit onto the operating table in the catheterization laboratory.

Further, the X-ray mapping technology used to monitor the movement of the catheter through the groin is not generally successfully in the extremely obese.

The radial arm approach is far more useful and practical. But the technique is not widely used in the United States, where only about 2 per cent of percutaneous coronary interventions (PCIs)—insertion of a catheter carrying a balloon and stent—are performed using the radial artery.

Analysis by his research team examined a select group of 48 patients who had an average BMI of 46. The analysis showed that 87 per cent of the patients were able to return home within 24 hours, meaning this was a safe procedure for the extremely obese.

Dr. O'Brien said a larger analysis is needed. His team is now studying results from 21,000 patients who have undergone PCI at the Heart Institute. Of that group, 12 per cent have had the radial artery technique. A better understanding of the anatomy of these patients is needed and further results will be announced at a later date.

MORE INFORMATION ONLINE

Links in the electronic edition at www.ottawaheart.ca/thebeat/

- See Dr. Edward O'Brien's bio page

UOHI AT AHA 2010

Therapeutic Hypothermia


Dr. Michel Le May

Results showed 69 per cent of patients survived and had an average hospital stay of about 14 days.

Dr. Michel Le May, Director of the Coronary Care Unit at the Heart Institute, discussed early results of research using therapeutic hypothermia in the most severe heart attack patients.

This approach involves cooling the body temperature to the 32 to 33 degree Celsius range to protect the heart from further damage after cardiac arrest. It has the potential to improve patient survival. His preliminary results looked at 26 patients brought to hospital with cardiac arrest and treated by emergency PCI.

Dr. Le May is also Director of the Regional STEMI Program and pioneered, in 2004, the emergency treatment of cardiac arrest patients using a new urgent diagnosis approach through the paramedic service. STEMI is an ST-elevation myocardial infarction, a serious heart attack that can be diagnosed quickly by paramedics.

Cooling by therapeutic hypothermia is an emerging area of clinical research that garnered quite a bit of attention at AHA this year. In the Heart Institute study, cooling was initiated within eight hours post-cardiac event. Results showed 69 per cent of patients survived and had an average hospital stay of about 14 days.

At some centres in the U.S., paramedic teams apply therapeutic hypothermia almost immediately in the field. The Heart Institute applies this technique in hospital, and Dr. Le May acknowledged that faster reduction in body temperature may prove more useful.

MORE INFORMATION ONLINE

Links in the electronic edition at www.ottawaheart.ca/thebeat/

- See Dr. Michel Le May's bio page
- Read more about heart attack and the Heart Institute's STEMI protocol